*Volume 7* **Neurology** *Number 6*

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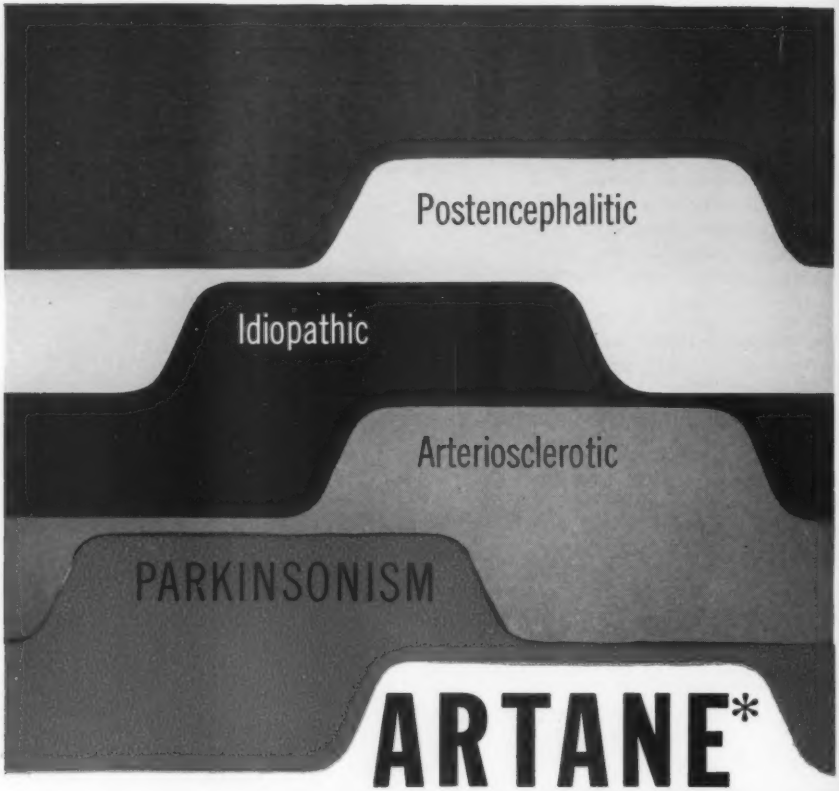


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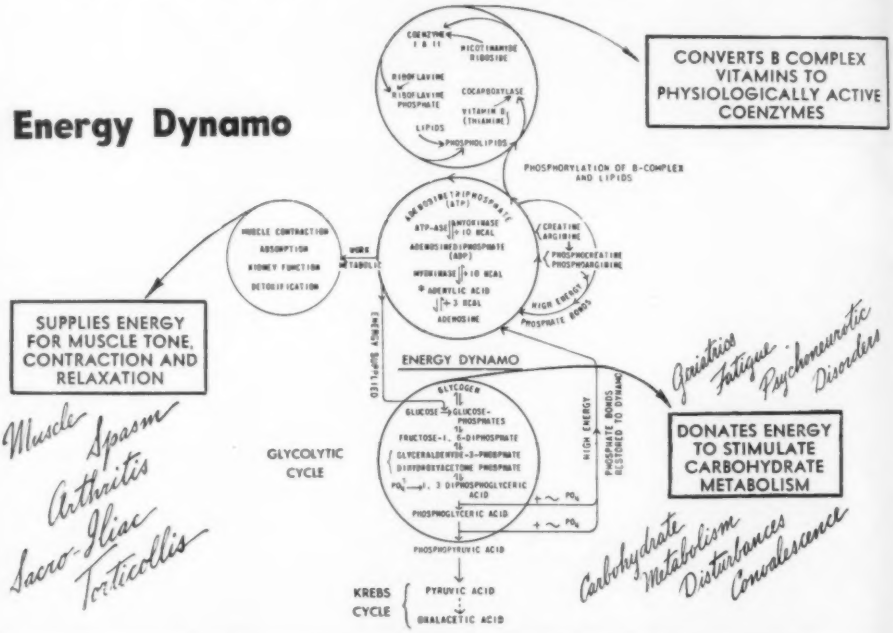


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Volume 7 Neurology Number 6

# Complications of Pneumoencephalography Associated with Internal Carotid Thrombosis

*Seymour Solomon, M.D. and Kevin D. Barron, M.D.*

Reported series of more than 500 cases reviewing the morbidity and mortality of pneumoencephalography attest to the safety of this procedure. The mortality rate has ranged from 0.2 to 1.6 per cent.[1–7] A large majority of the reported deaths have occurred in cases of brain tumor, and deaths of patients with cerebral vascular disease are rarely mentioned.[2,8] If the common but transient symptoms following pneuomencephalography are excluded, the morbidity resulting from air studies is so slight that such statistics were not even tabulated in the series noted above. Serious cerebral complications such as confusion and stupor were occasionally mentioned, but only three instances of focal cerebral sequelae were reported in the above reviews, which include a combined total of 7,604 cases. (The latter compilation excludes those series[3,6] which confined their observations to the mortality rate of pneumoencephalography.) It is of interest that two of the three cases were reported in Schuleman's[7] review of 572 pneumoencephalograms. The two cases to be reported were observed within a short span of time and suggest that significant morbidity may be greater than has been realized.

Specific evaluation of the hazards of pneumoencephalography in the presence of cerebral vascular disease is not to be found in the literature. Statements can be found, however, which set forth the belief that air studies are more hazardous in individuals with cerebral arteriosclerosis.[2,4,9,10] "Air studies in the face of carotid thrombosis" have been cited[11] as "carrying an impressive risk," and others[12] have warned of similar danger. Although these views are held and taught by most neurologists and neurosurgeons, except for an occasional single case report, the specific basis for these

From the division of neurology, Montefiore Hospital, New York City.

statements is not mentioned. We have gathered evidence of the hazards of pneumoencephalography relative to one special circumstance, occlusion of the internal carotid artery.

CASE REPORTS

*Case 1.* On December 28, 1955 a 55 year old right-handed, white milkman developed ill-described failing of vision and became confused. Later in the day he felt "dizzy" and noted numbness and weakness of the right arm. On December 29 he was admitted to another hospital where findings consisted of a minimal weakness of the right arm, confusion, dysnomia, and failure of memory for recent events. The patient was ambulant, moved all extremities, and carried on conversation. On January 3, 1956 pneumoencephalography was performed and interpreted as revealing slight symmetric cerebral and cortical atrophy. The patient tolerated the procedure well and on his return to the ward his status was unchanged; he spoke to his wife, indicated that he had a headache, and moved all extremities. At 7 a.m. the following day the patient was found to have a global aphasia and right hemiplegia. Past history revealed that patient had had a myocardial infarction in 1949, and in early 1955 diabetes mellitus had been discovered and easily controlled by diet.

The patient was transferred to Montefiore Hospital on February 17 where examination revealed a right hemiplegia and a right homonymous hemianopsia. He did not speak or utter a sound. Simple commands were comprehended, but he tired easily and failed in the execution of more complicated requests. Exophthalmometer readings failed to reveal exophthalmos.

Serologic tests for syphilis were negative in blood and cerebrospinal fluid. Complete blood count, urinalysis, blood urea nitrogen, and fasting blood sugar were normal. An electrocardiogram was indicative of healed posterior wall myocardial infarction. A chest roentgenogram revealed moderate enlargement of the left ventricle. Skull roentgenograms were normal and the calcified pineal gland was visible. Lumbar puncture revealed normal cerebrospinal fluid pressure. The cerebrospinal fluid protein was 208 mg. per cent in February and April 1956. An electroencephalogram was diffusely abnormal and showed slow-wave activity in the delta range emanating from all leads, but more prominent from the left side where voltage was depressed. Digital occlusion of the left common carotid artery for periods up to one minute was without effect on the electroencephalographic pattern.

On March 2 left common carotid percutaneous angiography was performed using Diodrast (figure 1). The internal carotid artery was found to be occluded at its origin. The external carotid vessels filled well, and opacification of a short segment of the intracranial internal carotid artery and the entire posterior cerebral artery was obtained by retrograde filling via the ophthalmic artery.

During April 1956 the patient sustained a deep thrombophlebitis of the right leg, complicated by a pulmonary embolus. Neurologic examination in July 1956 failed to reveal significant change when compared with that of January 1956.

*Case 2.* A 59 year old right-handed man was admitted to Montefiore Hospital on March 8, 1955. In October 1955 he had been involved in an automobile accident, in the course of which his head was violently extended, striking the cushioned seat, and then was flexed on his chest violently. He was "dizzy" for 15 minutes after the accident and his neck was stiff for several days. About 48 hours after the accident he noted that he could hear his "heart beat" in the left ear and that he had a throbbing left frontal headache. These complaints persisted intermittently until admission. In November 1955 he had two episodes of weakness and numbness of the right leg lasting several minutes. During December 1955 he developed episodes of tingling in the fingers of the right hand lasting several minutes, associated with involuntary movement of the right upper limb at the shoulder and elbow. These episodes continued several times per week to the date of admission. It was further noted that patient had been forgetful for several months. The past history revealed that he had had mild hypertension for at least seven years. A grade I epidermoid carcinoma of the right vocal cord had been removed in 1949 by laryngofissure and there had been no evidence of recurrence.

General physical examination revealed a blood pressure of 200/100, but was otherwise unre-

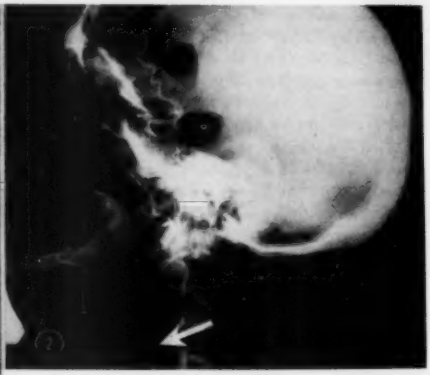

FIG. 1. Occlusion of the left internal carotid artery at its origin.

FIG. 2. Occlusion of the left carotid artery at its origin. Intracranial air is the residual of pneumoencephalography performed four days prior to arteriography.

markable. Neurologic examination disclosed a slight drift and pronation of the outstretched supinated right arm and slight weakness of the right hand grip. The flexor response to plantar stimulation of the right foot was less than on the left. Minimal ptosis of the left lid was described. The remainder of the neurologic examination was unremarkable. The carotid arteries were noted to be bilaterally "palpable and equal." Visual fields determined by perimetry revealed a slight peripheral right homonymous defect.

Routine blood count and urinalysis were normal. The fasting blood sugar and blood urea nitrogen were normal. A chest roentgenogram was unremarkable. Skull roentgenograms were normal and the calcified pineal gland was visualized. An electroencephalogram was within normal limits. Lumbar puncture revealed cerebrospinal fluid under normal pressure and the protein content was 72 mg. per cent. Blood and cerebrospinal fluid serologic tests for syphilis were negative.

On March 22 pneumoencephalography was performed with the injection of 110 cc. of air. The patient experienced headache but otherwise withstood the procedure well. The encephalogram showed suggestive evidence of mild cortical and cerebral atrophy. The blood pressure before and following air injection was 170/80. There was a fall in pulse rate to 48 per minute during the procedure, but this rose to a rate of 76 to 80 per minute within two hours. On conclusion of the procedure the patient was given oxygen by mask and caffeine sodium benzoate 0.5 gm. intramuscularly every four hours. When seen that afternoon and evening the patient spoke and moved all extremities, although he appeared drowsy. Oxygen was discontinued at 8:30 p.m. The patient's respirations, pulse rate, and blood pressure were recorded at hourly intervals through the afternoon, evening, and early morning of March 23. The pulse remained at about 80 per minute, the systolic and diastolic blood pressures did not vary significantly from pre-encephalography levels, and the respiratory rate was steady at 18 per minute. At 5:00 a.m. on March 23 the blood pressure was recorded as 180/80 and at 6:00 a.m. the reading was 190/80. Neurologic examination at that time revealed that the patient was aphasic and had a right hemiplegia. Pulsation of the left internal carotid artery at the angle of the jaw was less than the right.

On March 26 a percutaneous injection of

Diodrast was made into the left common carotid artery (figure 2). The left internal carotid artery was found to be occluded at its origin. There was excellent filling of the external carotid circulation on the left, and retrograde flow of dye into the intracranial internal carotid circulation by way of the ophthalmic artery was shown. An electroencephalogram on April 20 was abnormal by virtue of diffuse slow activity, with voltage depression and predominance of slowing over the entire left side of the head. The electroencephalographic pattern was not changed by digital occlusion of the left common carotid artery. Exophthalmometry did not reveal exophthalmos.

The patient made little recovery from the aphasia and hemiplegia and he was still grossly disabled three months after the onset.

### CASE COMMENTS

In both cases there was indication of vascular disease. Both patients tolerated the procedure very well, the new neurologic signs did not occur until many hours after pneumoencephalography, and in case 2 hourly blood pressure recordings failed to reveal hypotension.

There are other features of interest related to the more general problem of occlusion of the internal carotid artery. The collateral circulation through the ipsilateral external carotid via the ophthalmic artery was demonstrated in both cases. However, as judged by the relative lack of clinical change and by the lack of electroencephalographic change on attempts to occlude the ipsilateral common carotid, this collateral circulation was not clinically significant. Furtion was not clinically significant. In case 2 the history of neck trauma prior to symptoms of carotid artery occlusion suggests a causal relationship. The fact that the "carotids were bilaterally palpable and equal" in case 2 again indicates the unreliability of this simple test in determining patency of the internal carotid artery.

### REVIEW OF LITERATURE

Although we cannot be certain that all focal cerebral complications following pneumoencephalography are associated with occlusion of the internal carotid artery rather than thrombosis of the more distal branches of the arterial tree, the former appears more probable from our review of reported cases. We have been able to find only five cases of signs of occlusion of the internal carotid artery following pneumoencephalography. In addition, review of the literature reveals several random case reports which represent focal cerebral complications. Although description of the focal cerebral disease in the latter instances is too brief to attempt a precise localizing diagnosis, in the following case reports with adequate clinical detail thrombosis of the internal carotid artery is either definite or very probable.

1. Denny-Brown:[13]—A 59 year old man presented a two-week history of moderate right hemiparesis and slight aphasia. Transient shock occurred during pneumoencephalography and immediately upon recovery the patient was noted to have complete right hemiplegia, hemisensory deficit, homonymous hemianopsia, and aphasia. A left internal carotid artery occlusion was demonstrated by arteriography.

2. Taveras and Schlesinger:[11]—A 46 year old woman presented a six-month history of "twitching" of the left hand and face, followed by an organic mental syndrome. An arteriogram (right or left?) suggested a deep temporal lesion, but the pneumoencephalogram revealed "cerebral atrophy." Symptoms progressed to "total left hemiplegia" (within?) four days after the air study. Arteriography six months later revealed thrombosis of the right internal carotid artery.

3. Shapiro and Peyton:[14]—A 48 year old man presented an eight-week history of whistling in the ear synchronous with heart beat, followed by numbness of the right arm and leg and later minimal weakness in these extremities. Left internal carotid artery occlusion was established by surgical exploration, and later

simultaneous right carotid arteriography and pneumoencephalography were performed under general anesthesia. On recovery of consciousness the patient was aphasic and apraxic. This complication was attributed by the authors to arteriography; however, the latter was performed on the right side, while the subsequent symptoms indicated a left cerebral lesion. More likely, we believe, this was a complication of pneumoencephalography, although arteriography may have been a contributory factor.

4. Romano and Muller:[15] — A 62 year old woman presented a four-year history of intellectual impairment, numbness of the left hand, and failing vision of the left eye. Unusual symptoms were not noted during pneumoencephalography, but at the conclusion of the procedure her blood pressure rose and she developed transient stupor with weakness of the right side. There subsequently occurred stupor, right hemiplegia, coma, and ten days after the air study, death. Skull roentgenograms had revealed bilateral internal carotid artery calcification. The spinal fluid obtained terminally was grossly bloody. The possibility of cerebral hemorrhage was considered; however, occlusion of the internal carotid artery with massive cerebral infarction is just as likely.

5. Rosenheck:[16] — A 45 year old man complained of headaches for one year and difficulty in naming objects and numbness in the right arm for several days. Immediately following pneumoencephalography the patient reacted well except for increased drowsiness; on several occasions during succeeding hours, when asked how he felt, he replied with a reassuring nod of his head. The next morning he was found to have right hemiplegia and global aphasia from which recovery was slow. Although occlusion of the internal carotid artery was not proved, it is considered very likely. (The course of this patient after pneumoencephalography was very similar to that of our patients.)

The following are cases of focal cerebral disease following pneumoencephalography. The reports were too brief to suggest the sites of the lesions.

1. Stone and Jones:[17] — An "elderly" woman with hypertension underwent pneumoencephalography and subsequently died as a result of "rapid progress of her vascular occlusion."

2. Dixon and Ebaugh:[2] — " . . . . In one case a hemiplegia developed following encephalography."

3. Schuleman:[7] — A 41 year old male with convulsive disorder but without neurologic signs developed a transient aphasia two days after pneumoencephalography.

4. Schuleman:[7] — A 43 year old man with convulsive disorder but without neurologic signs developed a sudden left hemiparesis four days after pneumoencephalography. (The delay and sudden onset of signs after air studies make their relationship questionable.)

The incidence of cerebral infarction following pneumoencephalography is obviously small. There are several probable reasons for this. The fact that a relatively small percentage of air studies are performed in individuals over the age of 50 years (7 per cent and 7.5 per cent)[5,7] lessens the statistical likelihood of complications secondary to cerebral vascular disease. A second and major factor is that most patients subjected to air studies with symptoms and signs which later prove to have been caused by thrombosis of the internal carotid artery are individuals in whom the occlusion has resulted in a maximum zone of infarction and consequent severe neurologic deficit. The condition is not made worse, simply because a maximum defect is already present. Thus, in Johnson and Walker's review[18] of 101 cases of internal carotid artery thrombosis reported to 1951, air studies were performed in 44 patients, all of whom had severe neurologic disability (hemiplegia, aphasia, hemianopsia) prior to the introduction of air. In contrast, in our cases and in those reviewed above, only minimal defects were present prior to air studies. It must be admitted, however, that there are several reports in the literature[14,19] in which pneumoencephalography did not significantly affect the cerebral status associated with internal

carotid artery thrombosis, even though signs of the disease were relatively minimal prior to air studies.

PATHOGENESIS

We believe that internal carotid artery disease is the primary etiologic factor when focal cerebral signs follow pneumoencephalography. Causes of cerebral infarction other than major cerebral artery disease usually produce maximum signs at their onset, and further stress, such as air studies, would not be expected to have significant effect. Furthermore, common causes of cerebral infarction other than thrombosis of the internal carotid artery usually produce the typical picture of a "cerebrovascular accident" and the need for pneumoencephalography is rare. In contrast, occasional cases of internal carotid artery disease may simulate the early course of brain tumor, and it might be postulated that pneumoencephalography is performed more commonly under such circumstances than with other cerebrovascular diseases.

There are at least two sets of circumstances which have resulted in severe neurologic sequelae when pneumoencephalography was performed at a time when the clinical picture was associated with disease of the internal carotid artery. The simplest to explain and the one which might be expected most often is that associated with the relatively common development of mild shock during pneumoencephalography. Under these circumstances, symptoms of generalized weakness and faintness occur, with signs of pallor, cold sweat, tachycardia, hypotension, and occasionally syncope. It is well known that sudden drop of blood pressure from any cause may precipitate cerebrovascular thrombosis by virtue of relative stagnation of the column of blood in a diseased but anatomically adequate cerebral vessel. The case of Denny-Brown[13] previously cited would appear to be an example of such a set of circumstances and the untoward effects occur immediately. Oddly enough, most instances of focal cerebral sequelae of pneumoencephalography are not of this type, but rather develop hours after the air studies. Usually there is no history of sudden deterioration of the patient's condition, as the signs develop insidiously. The frequent blood pressure recordings in our case 2 substantiate the fact that complications can occur in the absence of a drop in blood pressure. The effect of pneumoencephalography upon cerebral blood flow and cerebral vascular resistance has not been studied, but it is probable that introduction of air produces some increase in cerebrovascular resistance with resultant reduction of cerebral blood flow.[20] The intracranial air may cause an irritative vasoconstriction of those cerebral vessels with which it comes in contact and, in turn, reflex vasoconstriction of deeper vessels may occur. Or the increased cerebrovascular resistance may be caused by an increase of the intracranial pressure, which is a frequent accompaniment of pneumoencephalography. In summary, focal cerebral lesions following pneumoencephalography may be due to diminished cerebral blood flow as the result of a lowering of the systemic blood pressure, but in most recorded cases increased cerebrovascular resistance appears to be the primary factor.

The exact pathogenesis of cerebral sequelae of pneumoencephalography is speculative. In cases of complete or partial occlusion of the internal carotid artery with minimal or transient cerebral

signs, the collateral circulation and/or the terminal arteries are barely able to sustain cerebral tissue. When the blood supply to this area of borderline adequacy is further compromised by diminished cerebral blood flow or increased cerebrovascular resistance, infarction occurs. A less likely possibility is the complete occlusion of a partially obstructed internal carotid artery which might occur when a drop in systemic blood pressure results in relative stagnation of blood in the diseased vessel.

## PROPHYLAXIS

With these theoretical considerations in mind, several possible applications with regard to the prophylaxis of focal cerebral complications of pneumoencephalography may be noted. Cases of internal carotid artery disease which are manifested by intermittent minimal signs or slow progression of signs are least easy to diagnose and most commonly confused with other cerebral diseases, such as brain tumor. Such patients may be subjected to air studies, and it is precisely these cases which are most prone to develop focal cerebral complications. A more thorough recognition of the manifestations of internal carotid artery disease will tend to prevent the use of pneumoencephalography under such circumstances. Caution in performing pneumoencephalography on patients with any evidence of vascular disease has been voiced in the past and is stressed at this time. Oxygen has been advocated as a method of quickly relieving the discomfort following pneumoencephalography by accelerating absorption of the intracranial air or other gas. It is known, however, that oxygen causes cerebral vasoconstriction. The resultant increase in cerebrovascular resistance may, in some cases, act as the added stress which significantly decreases the barely adequate collateral circulation. When pneumoencephalography has been performed on an individual in whom cerebrovascular disease is suspected, especially disease of the internal carotid artery, we believe that the benefits of oxygen inhalation are outweighed by the possible deleterious effects. The substitution of carbon dioxide-oxygen is suggested. Prophylactic anticoagulant therapy prior to pneumoencephalography in patients with cerebrovascular disease might be considered. The possibility exists that complete occlusion of the internal carotid artery may have already occurred prior to pneumoencephalography. Since the use of anticoagulants in carotid artery disease is still somewhat controversial, considering the difficulties and possible hazards of such medication, we believe that its prophylactic use in this special circumstance is not warranted.

## SUMMARY

Two cases have been reported and the literature reviewed to indicate the complication of extensive cerebral infarction following pneumoencephalography. Thrombosis of the internal carotid artery which has produced minimal focal cerebral signs is the most important factor associated with this complication. The pathogenesis is discussed and limited prophylactic measures are suggested.

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■ On the diagnosis of apoplexy I have only a very few observations to make. The strong disease is clearly marked by the symptoms which have been already described in its definition and history. Some persons, however, may possibly confound epilepsy with apoplexy, although these diseases very materially differ both in their nature and in their symptoms. In epilepsy, a person generally falls to the ground suddenly, as in apoplexy; but in the former disease we observe great agitation, with convulsion and spasmodic affection of the whole system, especially of the muscles of the face; whereas in the latter, the patient lies as if in a profound sleep, with stertorous breathing. The paroxysm of epilepsy is soon over; that of apoplexy generally lasts for some hours. Other symptoms by which these diseases may be distinguished will hereafter be described in my account of epilepsy.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

# Prognosis in Hemiballismus

*H. H. Hyland, M.D. and D. M. Forman, M.D.*

THE DISORDER known as hemiballismus is uncommon, although it has been recognized as a clinical and pathologic entity for more than 30 years. In a review of the literature up to 1947, Whittier[1] was able to collect only 60 cases. The clinical picture consists of abrupt, rapidly executed, extensive, involuntary movements of the limbs of one-half of the body which continue unceasingly during the waking hours but subside with sleep. The purposeless movements are distinguished from hemichorea by their large amplitude, flinging or kicking quality, and violence, with involvement of proximal muscles of the limbs more than the distal. They occur both when the limbs are at rest or when attempts are made to carry out voluntary movements. The muscles of the face, neck, and trunk on the affected side are often involved as well. Rarely, the abnormal movements are confined to one limb.

Pathologically the lesion is usually vascular, with either softening or hemorrhage being present. Other conditions, including metastatic tumors and granulomatous lesions, have occasionally been found. In most instances the contralateral subthalamic body of Luys is the site of the lesion, but some cases have been reported where this structure was found undamaged although its efferent or afferent connections were involved. In rare instances the lesions held responsible have been in the corpus striatum, the thalamus, or the postcentral gyrus.[2] Old and recent vascular lesions elsewhere in the brain are commonly found at autopsy, reflecting the generalized cerebrovascular disease that commonly exists in these patients.[3] However, the pyramidal tract is never found destroyed on the same side as the involved corpus Luysi, and it has been long recognized that hemiballismus cannot occur unless the pyramidal tract is able to function.

The prognosis in hemibalismus is generally considered to be bad. Most cases occur in elderly people who are already debilitated before being subjected to this exhausting disorder. Death takes place from progressive exhaustion, cardiac failure, or pneumonia.[4]

The number of cases that have been reported with spontaneous recovery is small and most authors take a very pessimistic view of the disease. Because of this and also because the condition is so

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alarming to the patient, his relatives, and the physician, radical measures in treatment sometimes have been employed such as limb amputation and destruction of the brachial plexus.[2] The administration of sedatives, hypnotics, and narcotics is the usual treatment, but their effect is not great unless given in dosage sufficient to induce sleep. In recent years various neurosurgical procedures have been advocated, including extirpation of the contralateral cortical area for the limbs,[5] subpial section of the cortex and subcortical white matter rostral to area 4,[2] cerebral pedunculotomy, and ventral quadrant section of the cervical cord.[7] Although these operations stop the involuntary movements, all but the last are followed by some degree of permanent hemiparesis. The use of chlorpromazine has recently been suggested as a method of treatment.[8]

The following group of 14 cases, seen in the Toronto area during the past ten years, is being reported because the incidence of spontaneous recovery is high and is in great contrast to the generally accepted opinion of the prognosis in hemiballismus. In those cases not seen by the authors personally, the diagnosis was made in all instances by experienced neurologists.

*Case 1.* A 57 year old hypertensive woman was seen in consultation on February 18, 1952, because of violent uncontrollable movements of her left arm and leg which had first appeared nine days previously on awakening.

On examination there were extensive, involuntary, rapidly executed movements of the whole left arm occurring almost continually. A less severe degree of the same thing existed in the left leg. There was no sensory or reflex change. She had a red, irritable looking rash on the left forearm, caused by friction from the involuntary movements.

The patient was treated with hypnotics; during the ensuing month the movements gradually lessened in frequency and severity, with complete recovery finally. On November 22, 1954 information was obtained that she had remained well and was carrying on normally.

In this case the hemiballismus developed as an isolated symptom suggesting a small discrete softening in the region of the right subthalamic nucleus or its

TABLE 1
14 CASES OF HEMIBALLISMUS

| *Case* | *Sex* | *Age* | *Affected Side* | *Associated Findings* | *Duration* | *Result* |
|---|---|---|---|---|---|---|
| 1. | F | 57 | Left | Hypertension | 6 wk. | Spontaneous recovery |
| 2. | F | 64 | Left | ——— | 3 mo. | Spontaneous recovery |
| 3. | F | 69 | Left | Signs of thalamic involvement | 10 wk. | Spontaneous recovery |
| 4. | M | 73 | Left | Hypertension, old right hemiplegia | 3 wk. | Spontaneous recovery |
| 5. | F | 80 | Right | ——— | 3 mo. | Spontaneous recovery |
| 6. | F | 67 | Left | Signs of thalamic involvement | 2 mo. | Spontaneous recovery |
| 7. | M | 72 | Left | Hypertension, myocardial insufficiency | 5 wk. | Spontaneous recovery autopsy—later |
| 8. | F | 77 | Right | Hypertension, angina pectoris, signs of thalamic involvement | 8 days | Spontaneous recovery with chlorpromazine |
| 9. | M | 68 | Left | Diabetes | 3 mo. | Spontaneous recovery with Promazine and chlorpromazine |
| 10. | M | 74 | Right | Auricular fibrillation, simultaneous left hemiplegia | 5 days | ? Spontaneous recovery autopsy—later |
| 11. | M | 84 | Left | ——— | 3 mo. | Chlorpromazine ineffective, recovery after pedunculotomy |
| 12. | M | 76 | Left | Diabetes | 18 days | Died—autopsy |
| 13. | M | 26 | Right | Onset after head injury | 5 days | Spontaneous recovery |
| 14. | M | 42 | Right | Multiple sclerosis—17 years | 6 wk. | Spontaneous recovery |

connections. Complete spontaneous recovery took place gradually within six weeks of the onset.

*Case 2.* A 64 year old woman suddenly developed gross involuntary movements of the left arm and leg, together with mental dulling and impairment of memory, four weeks before she was seen in consultation on January 11, 1946. During the previous week it had been noted that the movements had lessened somewhat in violence and frequency.

Examination showed her to be rather fatuous, emotionally unstable, and dull, with impaired memory for recent events. The left arm was in a constant state of violent, purposeless movement at all joints. The movements of the left leg had lessened materially, but there were occasional gross flexion and abduction movements at the hip and knee. There were no other findings on examination. The hemiballismus continued to improve during the next few weeks and had subsided completely within three months of the onset. The impairment of memory and emotional instability improved, but some residual defect remained. The only treatment was sedation to insure sleep at night.

In this case the mental and emotional disturbance which developed coincident with hemiballismus suggests a rather more extensive lesion than occurred in case 1. However, she made an equally complete spontaneous recovery from hemiballismus, although this took place more slowly.

*Case 3.* A 69 year old woman, a known hypertensive, was admitted to the Toronto General Hospital on April 4, 1947. Seven months, three months, and one week before admission, respectively, she had brief episodes of left-sided numbness involving the face and arm. With each of these a period of unconsciousness or mental confusion occurred. She had become very labile emotionally.

On the day following the last episode, after arising in the morning, there was sudden onset of uncontrollable movements of the left arm, articles flew out of her hand, and she was liable to strike herself. The movements were increased in severity by emotional upset but were absent during sleep.

Examination showed marked narrowing and tortuosity of the retinal arteries. Speech was somewhat explosive and slurred. Her emotions were very labile, with unmotivated laughter and crying. In addition to the almost constant, abrupt, and extensive involuntary movements of the limbs on the left side, there was a left lower facial weakness on emotional movements only, with hypotonia and hyporeflexia in the left arm and leg. A striking feature was the presence of a thalamic type of overreaction to pain and temperature on the left side with a loss of appreciation of finer stimuli.

Treatment with phenobarbital and hyoscine appeared to aggravate her emotional disturbance and it was stopped. She left the hospital against advice one month after admission, having shown little improvement, but her family doctor reported subsequently that improvement was more rapid thereafter and that the involuntary movements subsided completely about four weeks after discharge.

In this case the thalamus was evidently involved by the lesion, to account for the mimetic facial weakness and the sensory disturbance on the affected side. The hypotonia and hyporeflexia in the affected limbs were probably due to the lesion affecting termination of the cerebellorubrothalamic pathway in the anterior portion of the thalamus. The evidence of thalamic involvement suggests that hemiballismus was due to the softening affecting the afferent pathway to the subthalamic nucleus rather than that the latter was directly damaged. The patient undoubtedly had severe generalized cerebrovacular disease with lesions elsewhere in the brain to account for the previous episodes of disturbed consciousness and the pseudobulbar type of dysarthria with spontaneous laughing and crying.

*Case 4.* A 73 year old man was a known hypertensive who two years before had developed a right hemiplegia. He was admitted to the Toronto General Hospital on January 5, 1954 with a five-day history of violent, involuntary movements of the left arm and leg, which came on suddenly after mild exertion. During the five days at home he had been nursed on a mattress on the floor because of the severe

hemiballismus which had caused bad abrasions of his left arm and leg.

On examination there was weakness and spasticity of the limbs on the right side residual from the old hemiplegia. Both limbs on the left side were in an almost constant state of extensive, uncontrollable movement. Otherwise there were no significant findings. He was sedated heavily and nursed in two beds that were tied together.

After one week much improvement had occurred, and within three weeks the hemiballismus had ceased entirely. He remained in the hospital until March 1, 1954 because of attacks of respiratory and urinary infection, but there was no recurrence of the hemiballismus.

This elderly, debilitated man would probably not have survived had the severe hemisballismus persisted for very long, but it subsided spontaneously within three weeks. The onset after exertion, in the presence of hypertension, suggests that the lesion in this case may have been a small hemorrhage in the region of the right subthalamic nucleus.

*Case 5.* An 80 year old woman abruptly developed gross involuntary movements of the right side one month before she was seen in consultation on April 3, 1954. They were very severe and she would often strike her face with her constantly moving right upper limb. There had been some lessening in severity of the movements during the previous week.

On examination she was mentally clear and emotionally stable. The violent, flinging movements were most severe in the right arm but were present to a lesser extent in the right lower limb. She was well preserved mentally and physically for her age.

With good nursing care and sedation, her improvement continued and by June 1954 she was able to resume her normal activities, although liable to occasional mild involuntary movements. On November 23, 1954 it was learned that the patient was feeling very well and was entirely free of involuntary movements.

The hemiballismus here was probably due to a softening in the region of the left subthalamic nucleus. Improvement commenced three weeks after the onset, but movements continued with lessening severity for about three months. Recovery from severe hemiballismus was particularly gratifying in view of her advanced age.

*Case 6.* A 67 year old previously healthy woman was admitted to the Toronto General Hospital on August 14, 1956 with left-sided hemiballismus consisting of extensive, abrupt, flinging and kicking movements of the limbs and grimacing movements of the left side of the face. Some choreiform movements were also noted in the distal muscles of the limbs. The onset occurred on wakening the previous day, but for two or three days before that her family considered there was something "strange" about the left side of her body, although they were unable to describe it. Accompanying the hemiballismus was a hypersensitivity of the limbs on the left side; pressure or manipulation evoked an acute painful sensation that might last several minutes. There was no objective sensory loss. She was garrulous, flippant, and sarcastic but mentally clear.

Treatment with sedation and good nursing care during the first four days in hospital produced no change in the severity of hemiballismus. On August 18 Promazine, 25 mg. intramuscularly three times daily, was instituted. On the following day the dose was increased to 50 mg. It was discontinued on August 20 because her attendants considered that the hemiballismus had lessened materially. It did not get worse when the drug was discontinued. Phenobarbital, 1¼ gr. daily, was administered in divided doses and continued for several weeks. Improvement in hemiballismus and in the personality change was progressive, and on September 3 she was discharged from hospital. At this time she was able to walk but there were still some mild involuntary movements of the limbs. These movements had completely subsided seven weeks after discharge.

This patient recovered completely over a period of two months, the hemiballismus having been severe for only five days. It is questionable whether Promazine, which was administered for only two days, played any part in her recovery. The fact that hemiballismus did not become worse when Promazine

was discontinued suggests that the natural tendency to recovery was the determining factor and that this became operative coincident with the administration of the drug. The temporary hypersensitivity of the affected limbs suggests that the thalamus may have been involved by the vascular lesion.

*Case 7.* A 72 year old hypertensive man was admitted to Sunnybrook Hospital on December 9, 1953 because of prostatic hypertrophy with overflow incontinence. Three or four days previous to admission there was sudden development of involuntary movements of the left arm and leg.

On examination there were violent, involuntary movements of the left arm and leg without any other significant neurologic findings. He had learned to sit on his left hand and cross his right leg over his left in order to lessen the extent of the purposeless movements. He had signs of myocardial insufficiency and peripheral vascular disease.

Improvement was slow but steady, and by December 23, 1953 the hemiballismus was much less severe and subsided entirely within the next three weeks. He was discharged on February 7, 1954 with no evidence of hemiballismus or hemiparesis.

The patient was readmitted on February 15, 1954 because of sudden development of a left hemiplegia. There was in addition severe urinary tract infection and marked infection around the suprapubic cystotomy. He died on March 28, 1954.

At autopsy, the only lesion seen in the brain was an area of cystic softening with gliosis in the right hemisphere. This lesion was just above and lateral to the floor of the third ventricle but it had not extended to include the subthalamic nucleus. It involved the posterolateral portion of the thalamus and was encroaching on the posterior limb of the internal capsule.

The hemiplegia, which developed one month after recovery from hemiballismus, was evidently due to extension of the original area of softening to the capsular region. The right subthalamic nucleus was found to be intact at autopsy, but the lesion was so situated that it could have involved the afferent pathways from the thalamus by way of the globus pallidus to the subthalamic nucleus. This could explain the occurrence of hemiballismus, from which there was complete recovery one month before hemiplegia developed.

*Case 8.* A 77 year old hypertensive woman had suffered symptoms of arteriosclerotic heart disease with angina pectoris for the past five years. In 1954 she had an arthroplasty done for osteoarthritis of the hip, and during recovery she developed psychotic symptoms of a paranoidal nature from which she recovered spontaneously. On November 30, 1955, four days before admission to the Toronto General Hospital, she wakened at 2 a.m. with severe involuntary flinging movements of the right arm and leg accompanied by substernal pain.

On examination in the hospital the patient was mildly confused and expressed auditory hallucinations. There were violent, involuntary movements at the proximal joints of the limbs on the right side and the skin of the affected arm and leg was severely abraded. Some irregular involuntary movements were also occurring in the jaw muscles on the right side. Hypalgesia to pinprick with an overreaction to stronger stimuli on the affected side was noted on admission but disappeared a few days later.

The hemiballismus continued unchanged despite sedation during the next four days. At this time chlorpromazine, 12.5 mg. intramuscularly, was administered and followed by the regular administration of 25 mg. orally three times daily. Within 24 hours the involuntary movements had lessened markedly in extent and frequency and ceased entirely after three days. Hallucinations likewise disappeared. The drug was discontinued abruptly two weeks later, whereupon she again expressed auditory hallucinations and there was some return of the involuntary movements but of much milder degree than formerly. Chlorpromazine, 25 mg. three times daily, was resumed and gradually reduced over the next four weeks to 12.5 mg. twice daily. Attempts to reduce this dosage subsequently resulted in considerable irritability, so she was maintained on it and discharged from the hospital on February 2, 1956.

This patient, like cases 3 and 6, had evidence of thalamic involvement on the

affected side but it disappeared quickly. Its presence suggests that, here too, the lesion involved the fibers to the subthalamic nucleus from the thalamus by way of the globus pallidus rather than the subthalamic nucleus itself. Mild psychotic symptoms similar to those present with this illness were noted almost two years before when she was recovering from a hip operation. Therefore, the mental symptoms on this occasion were probably not directly related to the lesion causing hemiballismus. These symptoms, as well as hemiballismus, responded dramatically to chlorpromazine and both recurred, although to a milder degree, when it was discontinued four weeks later. Subsequently the drug was reduced to a very low dosage without return of the hemiballismus.

*Case 9.* A 68 year old left-handed man was a known diabetic for three years and was controlled by diet alone. On September 12, 1956 he fell, striking his head, but was not unconscious and was able to carry on afterward. The following morning on awakening there were involuntary movements of the left arm and leg which gradually increased in severity during the day, finally becoming violent and uncontrollable. He was given several intramuscular injections of chlorpromazine, 100 mg., at the Brantford General Hospital but the hemiballismus remained unchanged and he sustained severe contusions and lacerations through striking objects with the affected limbs. One week after the onset, fever developed and he was transferred to the Toronto General Hospital on September 20.

Examination on admission revealed a dehydrated elderly man who was mildly confused and disoriented. There were violent continuous involuntary movements of the left arm and leg. These were most severe at the proximal joints of the limbs where they were of an extensive flinging and kicking character. There were also grimacing movements of the muscles on the left side of the face. There was no weakness, reflex abnormality, or sensory impairment. The temperature was elevated to 101° F. and this was considered due to infection of the lacerations on his affected limbs which had developed underneath padded bandages applied a week previously. Promazine was given orally and increased to 100 mg. four times daily. Polysporin ointment was applied to the infected injuries on the limbs and penicillin was administered intramuscularly.

Within two days the hemiballismus was greatly improved and remained so during the next two weeks. Examination on October 5 revealed that he was mentally clear. The movements were no longer violent and they occurred only when he was disturbed or when the affected limbs were manipulated. Promazine was discontinued on this day; within 24 hours there was a recurrence of very violent, almost continuous movements of the left arm, leg, and face. With the return of these movements he again became confused and disoriented. On October 8 chlorpromazine, 50 mg. four times daily, was prescribed and within a few hours the movements lessened in severity. The following day his condition was the same as it had been when he was receiving the larger dose of promazine. On October 17 the chlorpromazine was reduced to 25 mg. four times daily, with no significant increase in the mild involuntary movements that were still present. He was discharged on October 28, at which time he was walking well and using his left hand for all ordinary purposes. An occasional extensive involuntary movement of the left arm and leg could be observed but these did not interfere with his activities. Chlorpromazine was further reduced to 12.5 mg. three times daily on November 4, 1956 and discontinued entirely on November 18. He was seen on November 25 and only an occasional movement of small amplitude was noted in the limbs.

Hemiballismus in this case was probably due to softening in the region of the subthalamic nucleus or its connections. That the initial improvement was due to Promazine was shown by the severe recurrence when it was discontinued two weeks later. Chlorpromazine in half the dosage rapidly reduced the movements to the previous degree and spontaneous recovery gradually took place, finally permitting discontinuance of the drug.

*Case 10.* A 74 year old man had suffered from arteriosclerotic heart disease for ten years and had been receiving digitalis for five years. On the day of admission to Sunnybrook Hospital, November 25, 1954, he developed difficulty with his speech and involuntary movements of the right arm and leg.

Examination showed that he was fibrillating, with an apex rate of 160. There was an expressive type of aphasia but he could comprehend and was cooperative. The right arm and leg were in a state of constant, violent involuntary movement. There were no other significant findings. About 15 minutes after the initial examination was completed, he developed a left flaccid hemiplegia with head and eyes deviated to the right side. The right-sided hemiballismus continued as previously.

The patient's condition remained unchanged during the next three days. On November 29 the hemiballismus ceased entirely. He was able to sit up in bed and to take nourishment, showing no paralysis of the right arm or leg. On December 2 he lapsed into a comatose state, the flaccid left hemiplegia being unchanged. There was now a grasp reflex on the right side. His condition deteriorated progressively and he died December 11, 1954.

At autopsy the cerebral arteries were moderately atheromatous. The brain showed small areas of recent softening in both parietal lobes. There was recent softening in the region of the right internal capsule, involving also the head of the right caudate nucleus. In the region of the left subthalamic nucleus there was a small area of softening. The nerve cells were atrophied and degenerated. There was considerable vacuolation and many cells stained indistinctly.

This patient with severe cardiovascular disease developed multiple areas of cerebral softening, probably due to emboli, in his terminal illness. One of these lesions involved the region of the left subthalamic nucleus, causing hemiballismus. The hemiballismus subsided spontaneously five days after onset, and it was possible to be sure that it was a true recovery and not simply the result of a superadded hemiplegia. However, the unusually abrupt cessation of involuntary movements so soon after onset raises the question as to whether another small, perhaps undetected, lesion had offset the effects of the softening in the left subthalamic nucleus, thus causing hemiballismus to cease. Therefore, we have doubt that this case represents a true spontaneous recovery, although we have no definite evidence to the contrary.

*Case 11.* An 84 year old man was in good health until the first week of September 1954 when he collapsed abruptly while climbing a flight of stairs. He remained unconscious or stuporous for an unknown length of time, following which there developed violent, uncontrollable movements of the left arm and leg accompanied by "pins-and-needles" sensations in the left arm, left side of the trunk, and left lower limb. During the ensuing ten weeks he was nursed at home, becoming progressively exhausted.

The patient was admitted to St. Michael's Hospital on November 16, 1954 in a dehydrated, malnourished condition. The skin of the left arm and leg was severely abraded. There were violent, extensive, involuntary movements of the left arm and leg, with some movements also on the left side of the face. These were continuous, ceasing only during deep sleep induced by heavy sedation. During light sleep some movements persisted in the left arm.

Treatment consisted of nursing care and heavy sedation. Reserpine, 2 mg. four times daily, was given for seven days without any benefit. On November 23 chlorpromazine, 25 mg. four times daily, was started and on November 26 this was increased to 50 mg. six times daily. Hemiballismus continued unchanged and it was evident that he was likely to die from exhaustion. On December 2 cerebral pedunculotomy was carried out, followed by complete cessation of the hemiballismus. The subsequent left hemiplegia improved greatly after a few days, but there remained some degree of permanent residual hemiparesis.

In this case hemiballismus was very severe and continued relentlessly for three months, showing no tendency to spontaneous improvement. Included in the treatment were reserpine and chlor-

promazine given in substantial dosage but they proved ineffectual. Cerebral pedunculotomy, carried out as a life-saving measure, brought about complete subsidence of hemiballismus.

*Case 12.* A 76 year old man was a known diabetic under apparently good control. On January 10, 1953, five days before admission to St. Joseph's Hospital, he was noted to show a change of personality and to behave abnormally. On the day before admission there was the sudden onset of violent, involuntary movements of the limbs on the left side and some involuntary movements of the left lower face. The movements were so severe that he fell out of bed and fractured his left humerus.

In addition to the severe left-sided hemiballismus, examination revealed a left homonymous hemianopia. Sedation had no effect on the severity of the involuntary movements and the patient's condition deteriorated progressively. Death occurred from bronchopneumonia on February 1, 1953, 18 days after the onset of hemiballismus.

Postmortem examination of the brain revealed old cortical softening in the left insular region extending forward over the lateral surface of the left frontal lobe. There was severe arteriosclerotic thickening of the basal cerebral arteries. A large recent softening in the subthalamic region on the right side, which contained a moderate recent hemorrhage, had destroyed the subthalamic nucleus and the adjacent portion of the substantia nigra. Only a few cells along the mesial borders of these structures had been spared. The internal capsule abutting on the lateral margin of the subthalamic nucleus was severely vacuolated due to edema and possibly early softening. The portion of the cerebral peduncle lying just lateral to the substantia nigra was similarly affected.

This is the only case in the series where death was directly attributable to hemiballismus. The presence of a hemorrhagic infarct in the region of the contralateral subthalamic nucleus was confirmed at autopsy. The additional finding of a homonymous hemianopia on the same side as hemiballismus may be accounted for by edema and possibly softening involving the optic radiation in the retrolenticular portion of the internal capsule.

*Case 13.* On October 2, 1954 a 26 year old man received a severe blow on the left temporal region from one of the flying parts of an exploded incinerator. He sustained a laceration of the scalp and was rendered unconscious for several minutes.

Neurologic examination at the Hamilton General Hospital later that day revealed no focal signs, but there was pretraumatic and posttraumatic amnesia of brief duration. Several hours afterward he developed continuous, violent, involuntary movements of his right arm and leg and side-to-side movements of his head, which stopped when he dropped off to sleep.

The hemiballismus was treated with hypnotics and during the course of the next four days the involuntary movements gradually subsided. The drowsiness and irritability attributed to concussion likewise improved. He was allowed out of bed on October 12 and was discharged on October 19 free of symptoms.

This case is of interest because cerebral trauma was the initiating factor in an otherwise healthy young man. It is assumed that he sustained cerebral contusion with edema or perhaps a small hemorrhage in the region of the left subthalamic nucleus, causing hemiballismus. An occasional case of hemiballismus following trauma has been reported previously.[5]

*Case 14.* A 42 year old man was admitted to Sunnybrook Hospital in March 1952 with various complaints, including increasing difficulty in walking and retention of urine. His illness commenced at the age of 25 in 1935 when he experienced onset of diplopia, dysarthria, and left-sided weakness. These symptoms recovered completely over a period of one year, but subsequently he had recurrences of neurologic symptoms usually confined to the limbs. The diagnosis of multiple sclerosis was made on his first admission to Sunnybrook Hospital in 1948, at which time his findings included some pallor of both optic disks, an ataxic gait, hesitancy and periodic retention of urine, emotional lability, hyperactive deep re-

flexes, absent abdominal reflexes and bilateral upgoing toes, slurring dysarthria, and incoordination of the left upper limb.

On readmission to Sunnybrook Hospital in July 1952, there were complaints of more severe disturbance of sphincter control and he showed some increased spasticity of the lower limbs with impaired vibration appreciation and mild defect of postural sense in the toes. While in hospital there developed over a period of 24 hours a right-sided hemiballismus with extensive, flinging, involuntary movements of the arm and leg. The violence of the movements lessened after five days but he was confined to bed for one month. It had subsided completely six weeks after the onset.

This case is of great interest because in cases of multiple sclerosis it is very rare for the pathologic process to involve the subthalamic nucleus or its connections and produce hemiballismus. However, the manner of onset, at a time when symptoms referable to the spinal cord were increasing, strongly suggests that multiple sclerosis was responsible. This patient was re-examined recently (February 1956). He is now a very advanced case of multiple sclerosis, but he shows no evidence of any cardiovascular or neoplastic disease that could be implicated as a cause for the hemiballismus four years ago.

DISCUSSION

It will be seen that, with the exception of cases 13 and 14 where cerebral trauma and multiple sclerosis respectively were the causative factors, the patients were all in the older age group. The average age of these 12 patients was 72 years and vascular lesions of the brain were considered responsible in all instances. In three cases the lesion was demonstrated at autopsy. Four patients had hypertension and two were diabetics. In several there was clinical evidence of myocardial disease and/or diffuse cerebrovascular disease. Thus, for the most part, these patients were elderly and debilitated when subjected to the exhausting hemiballismus.

It seems certain that few elderly patients would survive many weeks of hemiballismus but for the fact that the involuntary movements lessen in severity while dozing and cease completely with deep sleep. This allows some respite during the severe phase of the illness if effective sedation can be provided. In this series the usual experience was for the movements to lessen in severity after one to three weeks and to subside completely during the next four to nine weeks. When spontaneous recovery took place it was gradual, and any tendency for the violence of the involuntary movements to lessen within a few weeks of the onset gives reason to believe that in time they will subside entirely. There was only one case (case 10) in this series where cessation of the hyperkinesis was rather abrupt, occurring five days after the onset. This patient had a number of cerebral softenings due to cardiac emboli, including that which had destroyed the subthalamic nucleus. While no superimposed hemiplegia had occurred, it was thought possible that another, perhaps unrecognized, vascular lesion may have involved other pathways and in some manner offset the effect of the damage to the subthalamic nucleus, thus causing the hemiballismus to stop. In view of this possibility, it is doubtful if this case should be considered an example of spontaneous recovery.

Recovery probably occurs through a readjustment in function of the extrapyramidal structures and their cortical and brainstem connections, which compensates for the imbalance caused by damage to the subthalamic nucleus or its connections. It is possible that, when

hemiballismus results from interference with the connections of the subthalamic nucleus and the latter itself is not damaged, the chances of readjustment leading to spontaneous recovery are much greater. We have clinical evidence suggesting that this was the situation in three cases (cases 3, 6, and 8). These patients showed clinical signs of thalamic involvement coincident with the development of hemiballismus, and it is assumed that the lesions were affecting the afferent fibers from the thalamus to the subthalamic nucleus by way of the globus pallidus. In another instance (case 7) where the hemiballismus subsided spontaneously, death took place two months later. At autopsy the subthalamic nucleus was found to be intact, but the lesion was so situated that this pathway could have been involved.

In most textbook descriptions of hemiballismus, the opinion is expressed that the prognosis is very bad. It has been stated in recent reviews of the subject that "spontaneous recovery is not to be expected,"[2] "The prognosis in hemiballismus is bad. Spontaneous recovery is rare."[3] On the assumption that spontaneous recovery is unlikely, it has been suggested that operation should be urged for all cases as a semi-emergency measure.[2] We consider this unjustified because of our observations in this group of cases which indicate that neurosurgery should be delayed until it becomes evident that spontaneous recovery is unlikely to take place. In some instances the failure of the disease to show any signs of remitting after several weeks, along with deterioration in the patient's general condition due to exhaustion, justifies surgical intervention as a life-saving measure (case 11).

It seems probable that hemiballismus is more common than is usually supposed, since 12 of this group of cases were seen in the Toronto area in the past four years. Much of the earlier interest in the disease was in the pathologic findings and the more recent interest has been mainly in the surgical treatment. There is a possibility that many cases in which spontaneous recovery has occurred have not been recorded in the literature. While the high recovery rate in our small group could be exceptional, there is reason to believe that the outlook is, in general, much better than is usually stated.

Medical treatment consists of good nursing care, measures to prevent injury to the involved limbs, the maintenance of adequate nutrition, and the use of heavy sedation with hypnotic drugs to ensure sleep. Chlorpromazine was reported by Tatlow and co-workers[8] to have a dramatic effect in stopping the involuntary movements in a case of hemiballismus. We obtained a similar rapid improvement with chlorpromazine in case 8, and with Promazine as well as with chlorpromazine in case 9, the hemiballismus recurring with its former severity when the drugs were temporarily withdrawn. In case 9 chlorpromazine was found to have a stronger action than Promazine, since the former drug proved to have equal effect with only half the dosage. However, there was one other case in our series (case 11) where chlorpromazine was used without any benefit. Here the drug was not given until ten weeks after the onset, whereas in the former cases it was administered early in the course of the disorder. It seems unlikely that late administration is the explanation of its ineffectiveness in case 11. If its action is to depress abnormal impulses originating in the ex-

trapyramidal system which are released when an inhibiting influence of the subthalamic nucleus is removed, duration of symptoms should not be very important. Further experience with chlorpromazine in the treatment of hemiballismus will be necessary before any sweeping conclusions can be drawn about its efficacy in the condition, but it seems to offer promise in some cases at least and it should always be tried.

## SUMMARY AND CONCLUSIONS

Fourteen cases of hemiballismus are reported. In one young patient the condition became manifest after cerebral trauma, and in another it developed at the time of an exacerbation of long-standing multiple sclerosis. The other 12 patients were all elderly and the hemiballismus was considered to be a result of cerebrovascular disease.

In 12 cases the hemiballismus subsided spontaneously, treatment consisting of good nursing care, in most instances combined with the use of hypnotic drugs. In two cases where chlorpromazine was used the prompt relief of symptoms suggested that it had a specific effect in controlling the hemiballismus, but in one other case it was ineffectual. In two patients hemiballismus failed to subside spontaneously. One died with the disorder and the other would probably have died had cerebral pedunculotomy not been performed successfully.

It is suggested that spontaneous recovery from hemiballismus is more likely to take place if the lesion involves the afferent connections of the subthalamic nucleus and the latter escapes destruction. In four cases of this series there was evidence that this had occurred. In one patient who died two months after recovery from hemiballismus, autopsy revealed the lesion in this situation. There were three other patients with spontaneous recovery who had signs of thalamic involvement developing coincident with the hemiballismus. The occurrence of these manifestations together makes it seem probable that hemiballismus was caused by damage to the afferent connections rather than to the subthalamic nucleus itself.

The high incidence of spontaneous recovery from hemiballismus in this series is contrary to the generally accepted opinion of the prognosis in this disorder. The results suggest that many patients will recover with conservative measures alone. Neurosurgery should be necessary only in cases with a long unremitting course or where deterioration in the patient's condition due to exhaustion renders it essential.

The authors wish to express their thanks to Drs. H. J. Barnett, E. Calhoun, W. J. Horsey, D. Levy, J. C. Richardson, and J. A. Walters for allowing their cases to be included in this presentation.

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# Radioactive Iodinated Human Serum Albumin in the Diagnosis of Intracranial Mass Lesions

*E. S. Gurdjian, M.D., J. E. Webster, M.D., H. R. Lissner, W. G. Hardy, M.D. and D. W. Lindner, M.D.*

RADIOACTIVE iodinated human serum albumin has been used in our laboratory during a period of 18 months from September 1954 to April 1956 as an aid in localizing brain tumors in 116 patients who have had 120 surveys. Of these surveys, 49 were in patients who had a verified brain tumor and 25 in patients who had cerebrovascular disease. In a number of cases the removed tumor was studied for its relative radioactivity. Of the remaining 46 surveys, 19 were performed for headache problems, seven for convulsive disorders, six for degenerative brain disease, five for pseudotumor cerebri, four for post-traumatic complaints following head injury, two for multiple sclerosis, and two for ataxia problems.

## METHOD

One and a half to two days prior to injection of the radioactive solution, the patient was started on Lugol's solution, 15 drops three times a day, administered for seven days. Five hundred microcuries of iodine 131 (Risa) was injected into a brachial vein approximately 24 hours before making the survey. In ten patients surveys were made at times ranging from seven hours to eight days after the injection. Except for the large decay which took place with a longer time period, the variation in time between the injection and the counting did not affect the results obtained in our tests.

The survey was made using a bismuth-coated GM tube (Tracer-Lab TGC-8) having an efficiency for the iodine 131 gamma radiation of four to five times that of an ordinary GM tube. The GM tube was encased in a cylindrical lead shield four inches long and having half an inch wall thickness (Tracer-Lab T-6). After a number of preliminary experiments it was decided to mount the tube window flush with the end of the lead shield and to cover it with a lead filter one-eighth inch thick. The lead filter served to screen out a large percentage of the lower energy scattered radiation.

Fourteen positions were defined on each side of the head and seven along the midline (figure 1). A count rate meter was used to indicate the activity which was recorded by a one milliampere M Esterline Angus recorder. Readings were taken alternately on opposite sides of the head for easy comparison.

From the Wayne State University neurosurgical service, Grace Hospital and Detroit Memorial Hospital, Detroit, Michigan.
Aided by the Hammers' Fund.

THE GRACE HOSPITAL ISOTOPE LABORATORY

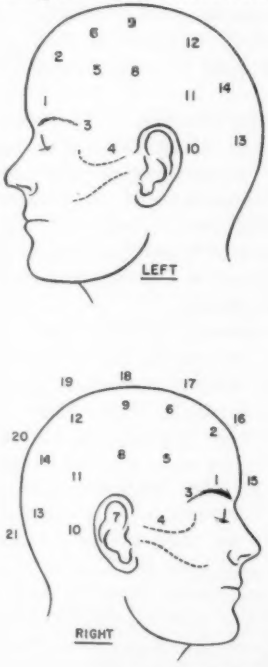
Date ..... 19 .....

Time .....

Patient .....

Dose ..... Date and Hour .....

Background .....




| POS. | FIRST COUNT RIGHT | FIRST COUNT LEFT | CORRECTED COUNT RIGHT | CORRECTED COUNT LEFT | % VAR. |
|---|---|---|---|---|---|
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | | | | | |
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| 21 | | | | | |
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FIG. 1. Positions used to record radioactivity for localization of intracranial lesions.

It was found necessary to obtain records from two to three minutes in length for each position to provide reliable values of count rate, which was read to plus or minus 50 cm.

Using the previously described dosage and counting geometry, a maximum count rate of from 1,600 to 1,800 counts per minute was generally obtained. This value was above the usual background count of 200 per minute. From an analysis of the results obtained, it was determined that an actual difference of 200 counts per minute from left to right was necessary before the presence of a tumor could be established with certainty. In some cases tumors were present with a difference from left to right of 150 counts per minute, but in many cases differences of this magnitude existed with no tumor present.

As a precaution, the patient's hands

and arms were kept away from his head while the survey was made since the reading was markedly increased when the arm or hand was brought alongside the GM tube.

Portions of the tumor and the adjacent brain were checked for radioactivity after removal in a number of cases. These tests were made by placing the specimen under a GM tube in a cast-iron shield. The samples were carefully weighed before counting and the count rate per gram of tissue was computed, using the same counting geometry for all tests. In this way the relative activity in tumor and brain was determined.

## RESULTS

The results of our studies can be divided into the following four groups: *group 1*, in which the position of the tumor was properly located by the survey and confirmation was obtained by operation or autopsy; *group 2*, in which no tumor was diagnosable from isotope studies but the presence of a tumor was confirmed by air studies, angiography, and/or operation; *group 3*, in which a positive indication of a tumor by the survey was not corroborated by air studies or angiography; and *group 4*, in which surveys were negative for a tumor and this was corroborated by air studies and/or angiography and other studies. A more detailed discussion of findings will be given in the following few paragraphs.

*Group 1.* Radioisotope surveys correctly diagnosed 27 of 49 studies, or 55 per cent. Tumors localized correctly were 13 glioblastomas out of 19, 10 astrocytomas (grades 2 and 3) out of 13, one meningioma out of 5, one metastatic tumor out of three, one pinealoma, and one medulloblastoma.

Of the 49 surveys, 39 were made in patients with hemispheric lesions, seven with posterior fossa tumors, and three with supraoptic masses at the base of the frontal lobes. Twenty-five of 39 hemispheric lesions were correctly diagnosed, or 64 per cent. Only two of the

TABLE 1
DIAGNOSIS OF TUMOR BY RADIOISOTOPE ACCORDING TO TYPE

| *Type of Tumor* | *Correctly Diagnosed* | *Not Correctly Diagnosed* |
|---|---|---|
| Glioblastoma | 13 | 6 |
| Astrocytoma (grades 2 and 3) | 10 | 3 |
| Oligodendroglia | 0 | 2 |
| Meningioma | 1 | 4 |
| Cerebellopontine angle tumor | 0 | 3 |
| Primary neoplasm of optic chiasm | 0 | 1 |
| Chromophobeadenoma of pituitary | 0 | 1 |
| Metastatic tumor | 1 | 2 |
| Pinealoma | 1 | 0 |
| Medulloblastoma | 1 | 0 |
| Total | 27 | 22 |

TABLE 2

| 27 *Correctly Diagnosed* | | 22 *Incorrectly Diagnosed* | |
|---|---|---|---|
| Hemispheric lesion | 25 | Hemispheric lesion | 14 |
| Posterior fossa lesion | 2 | Posterior fossa lesion | 5 |
| | | Supraoptic and base of frontal lobes | 3 |

seven posterior fossa tumors were diagnosed correctly. The three tumors above the optic area and at the base of the frontal lobes were all completely missed. A relative increase in the accuracy of the method for hemispheric lesions thus becomes apparent.

*Group 2.* This group consisted of brain tumors diagnosed incorrectly by the survey. Two of three metastatic tumors were incorrectly diagnosed. One chromophobe adenoma of the pituitary, one primary neoplasm of the optic chiasm, and a supraoptic meningioma were incorrectly diagnosed. Five of seven posterior fossa tumors were incorrectly diagnosed. Four meningiomas out of five were missed, and three astrocytomas (grades 2 and 3) out of 13 were incorrectly diagnosed, as were six glioblastomas out of 19.

A low rate of accuracy occurred with posterior fossa tumors and deep seated tumors, especially those at the base of the brain.

One case was rather unusual. This patient had two surveys several months apart. At the first, the presence of a tumor was indicated but this was not confirmed by other studies. Several months later another survey was made with no indication of the presence of a tumor. However, air studies and angiography indicated the tumor which was removed from the region where the first isotope study placed it. No definite explanation for this behavior has been found.

The excised tumors were studied for radioactivity content in 21 cases. The activity readings in the tumors were generally consistent with the results obtained when attempting to locate the tumor originally. When the difference in counts between the tumor and brain was high the tumor was readily located, but when a small difference existed localization was not possible. In a number of tumors checked there was a relatively high uptake of radioactivity on the surface of the tumor, with practically no activity present beneath the outer layer. Under these circumstances, in the case of a large tumor, the average activity of the entire tumor may be no different from that of the brain with no possibility for localization. This may account for the experience of locating a tumor on the first survey and finding no evidence of it on a survey several months later. In such a case, when the tumor is small and the radioactivity is mainly on its surface, this surface constitutes a larger proportion of the whole than when the tumor becomes very much larger several months later (the same situations existing, that is the uptake being mainly on the surface of the tumor).

*Group 3.* There were seven cases in which a definite indication of an increased amount of radioactive uptake suggested the presence of a tumor, but this was not corroborated by air studies and angiography. One in this group was a case with a significant increase in radioactive uptake noted in the occipital area when the tumor was in the frontal region on the same side. The remaining six were not thought to have a brain tumor or any other mass lesion. It is difficult to explain the findings in group 3. It is conceivable that there may be other reasons for a change in the blood-brain barrier permitting the accumulation of the radioactive material in areas not necessarily malignant. It is noteworthy that when a subdural hematoma had been correctly diagnosed by radioactive survey, the removed hematoma

had little or no radioactive content, suggesting that compression by the mass resulted in an abnormality of the underlying surface with resultant radioactive uptake. Certain chemicophysical changes in normal patients may be responsible for such increased radioactive uptake.

*Group 4.* Group 4 included 64 instances of negative results. Then differences in count rate from right to left were 150 or less, the rate differential which has been found to be insignificant for localization of brain tumors. In this group there were 25 cases of vascular disease of the nervous system which are discussed in greater detail.

Of the 25 cases, two had aneurysms with active bleeding. One was paralyzed in the left half of the body. Both had normal studies. There were three cases of acute intracerebral hematomas; one had no significant change on either side and in one there was a correct localization – if one were to assume a count differential of 100 to 150 to be of value; another was localized incorrectly. Again, with the assumption that the count differential of 100 to 150 would be of value, there were ten instances of high count on one or the other side in 20 cases with the "stroke" syndrome. Among these, six were on the side of the lesion and four were on the opposite side from the lesion which was located by clinical means.

There were 13 patients with intractable headaches whose studies were negative by this technic. There were seven with a convulsive disorder whose surveys were also negative. There were five cases of pseudotumor cerebri with choked disk in which the air studies were normal and exploration in some also resulted in no tumor localization. In eight cases of degenerative disease of the brain (four of presenile dementia, two of brain atrophy, two of multiple sclerosis), the radioisotope surveys were negative. The same was true in four instances involving post-traumatic complaints of headache and dizziness.

## DISCUSSION

In 1947 Moore[1] reported the use of fluorescein in the differentiation of normal and malignant brain tissue. Since then there has been a great deal of work done with radioactive isotopes for brain tumor localization. Among the isotopes commonly used are radioactive iodinated human serum albumin and di-iodofluorescein ($I^{131}$), potassium ($K^{42}$), phosphorus ($P^{32}$), and arsenic ($As^{74}$). Among the methods of recording should be included recording from a single or multiple geiger counter and from scintillation counters. Both direct counting and coincidence counting have been used. Risa (iodine 131) has been used by Peyton and co-workers,[2] by Rushton, Svien, and Baldes,[3] and by Dumbar and Ray.[4] The papers of Dumbar and Ray and Rushton and associates are particularly interesting. There were 30 cases of hemispheric tumors reported by Dumbar and Ray and correct localization was obtained in 76 per cent, whereas in the total number of cases accuracy was about 61 per cent. In our material above reported, hemispheric tumors have been diagnosed with a higher degree of accuracy (66 per cent) than the entire group (55 per cent). When one compares the type of tumors correctly diagnosed by Dumbar and Ray with those of Rushton and associates, as well as our own findings, there is a wide variation in tumor type versus localization. Dumbar and Ray reported localization in nine out of ten glioblastomas, three out of five astrocytomas, six out of seven

meningiomas, and five out of eight metastatic tumors. Rushton and associates stated that five of 18 astrocytomas were correctly localized, two were falsely localized, and 11 were not localized. In our own group, 13 of 19 glioblastomas were correctly localized, 10 astrocytomas (grades 2 and 3) of 13 were correctly localized, and only one of five meningiomas. Rushton and associates found two of six cases of metastatic tumors to be correctly localized.

Dumbar and Ray reported 11 nonhemispheric tumors, with only two correctly localized. They rightly concluded that the use of isotope localization is of limited value in the posterior fossa.

Among vascular lesions, aneurysms gave negative results in the cases of Dumbar and Ray and of Rushton and associates and we have had the same experience. Four subdural hematomas were correctly located by Dumbar and Ray, with an increase of 20 to 30 per cent of radioactive uptake over the mass compared with the opposite side. It was rather interesting to note that the clot itself had no radioactive uptake. Rushton and associates were able to locate correctly two of three subdural hematomas. In a case of a bilateral subdural hematoma there was a higher count over the right temporofrontoparietal area, and in a case in which there was no evidence of radioactive uptake 100 cc. of liquefied clot was removed. Farris, Pertek, and Cohn,[5] using Risa, have found a general accuracy of 60 per cent for the localization of brain tumors. High counts were obtained among six cases in their group, suggesting a brain tumor when none was present. We have had the same experience with six cases in this study.

The use of arsenic$^{74}$ has been of value in the experience of Sweet and Brownell.[6] Using an automatic scanning device after intravenous injection of positron-emitting arsenic$^{74}$ as a sodium salt, the tumor position is recorded pictorially with an accuracy of about 75 per cent. A higher degree of accuracy for brain abscesses was obtained. Only one of five patients with cerebral thrombosis showed abnormal scans. The best results by this method were seen in meningiomas – only one out of 24 was missed; four of 42 cases of glioblastomas were missed, and four of 13 patients with metastatic carcinoma were incorrectly diagnosed. Among blood vessel abnormalities, thrombosis or hemorrhage was correctly diagnosed in three of 18, arteriovenous malformations in one of five, subdural hematoma in two of four, and subarachnoid hemorrhage and/or aneurysms in one of four cases.

Although Risa has been disappointing for the localization of brain tumors, $P^{32}$ injected intravenously in patients with brain tumors and recorded with a Robinson-Selverstone geiger counter probe was found to correctly localize 46 of 50 tumors by Schneider, Pentek, Freeman, and Farris.[7] Others have reported similar results. A high degree of accuracy is obtained with this method, and this has been our experience also. The use of $P^{32}$ and the probe counter should be available in all neurosurgical operating rooms. Its value for certain deep-seated neoplasms cannot be denied.

SUMMARY

1. Our experience with Risa has been disappointing and this agrees with the reports of others.

2. However, such studies should be continued with other radioactive substances toward obtaining a clinically

useful test. Although $P^{32}$ is excellent for direct counting in the operating room, a comparable substance to be used in preoperative surveys has not yet been found.

3. Because of the early use of a simple test in the course of a progressive disease, negative findings may be expected early. Repeated examinations later may locate the lesion accurately.

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■ Reeling is the earliest motor symptom of tumour of the cerebellum. It is not the gait of locomotor ataxy, nor that of paraplegia. It is like the walk of a drunken man. It occurs in some cases of ear disease – often acutely in paroxysms (Ménière's disease), or sometimes chronically. It is essentially a swaying of the trunk from back to front and from side to side. It is masked in some slight cases by the patient's walking with his legs apart; by this means small inclinations of the trunk are neutralized. The gait is worse when he walks with closed eyes. In early stages, in slight reels, I believe the true fault is paresis of movements of the spine answering to the swaying of the trunk. The legs act erratically, but in an early stage they are blameless; they act erratically because they have to "run after" the trunk, to prop it up in its various over-inclinings. The legs, often blamed, are really doing more than their duty. In cases of paralysis of the extensors of the feet the patient lifts his legs highly. To a layman his defect would appear to be that of lifting the legs highly. But this movement is necessitated by the paralysis of the extensors, and to blame the leg in an early stage of cerebellar reel would be like blaming the leg-lifting movement in paralysis of the extensors of the feet. If the true fault in cerebellar reeling be paresis of the movements for bracing up the spine, we see that the reel compares with hemiplegia; the essential fault in the reel is a partial paralysis.

J. Hughlings Jackson in *On Tumours of the Cerebellum*, published in 1881.

# Lesions in the White Matter in Acute Poliomyelitis

*Irwin Feigin, M.D.*

UNLIKE most viral infections of the nervous system, poliomyelitis is generally considered to be a disease in which the pathologic process is specifically limited to the gray matter. Pathologic reports describing lesions in the white matter are rare.[1–3] Although pain and hyperalgesia are frequently noted, clinical reports describing sensory loss suggestive of a lesion in the white matter of the cord are uncommon.[4,5] Sensory alterations may also be expected with involvement of the dorsal root ganglia or of internuncial sensory neurons.[6–8]

In this paper, lesions in the white matter of the cord are described in four cases of acute poliomyelitis.

*Case 1.* A 29 year old woman developed a sore throat one week before death, headache, neck pain, nausea, and vomiting four days before death and fever and aching pains in the legs two days before death. On the day preceding death, she was admitted to the hospital in stupor, with a flaccid quadriplegia, tachypnea, cyanosis, and high fever. She expired the following day while a tracheotomy was being performed. There were no clinical observations of sensory loss.

Autopsy revealed visceral congestion and pulmonary edema. The brain revealed no gross changes other than congestion. Microscopically, a slight generalized lymphocytic infiltration of the leptomeninges was noted. The ventral gray matter of the spinal cord revealed focal and diffuse collections of microglial cells and a few polymorphonuclear cells and lymphocytes. Some of the focal collections of cells appeared of the size and shape of neurons and, presumably, marked the site of neuronal necrosis. Intact neurons were present in adjacent areas. The substance of the gray matter was diffusely rarefied and, where this was most severe, contained a great many microglial phagocytes diffusely distributed. The blood vessels of the ventral gray matter were congested and contained a great many lymphocytes and a few phagocytes in the perivascular spaces. Similar but less intense changes were noted in the dorsal gray matter of the cord, brainstem, basal ganglia, and cerebral and cerebellar cortex.

The most frequent lesion in the white matter consisted of an infiltration of the perivascular spaces by lymphocytes and a few phagocytic cells. In the cord such lesions were most severe in the region adjacent to the severely affected gray matter, but were not limited to such regions.

Of special interest was the presence of focal collections of microglial cells and a few polymorphonuclear cells in each dorsal column just beneath the leptomeninges (figure 1). These were approximately 0.5 mm. in maximal diameter. Small blood vessels with hypertrophic walls infiltrated by inflammatory cells were present within each area, as well as in adjacent areas. These were neither necrotic nor thrombosed, but adjacent capillaries were thrombosed. The cerebellum contained a similar focal inflammatory lesion in the white matter adja-

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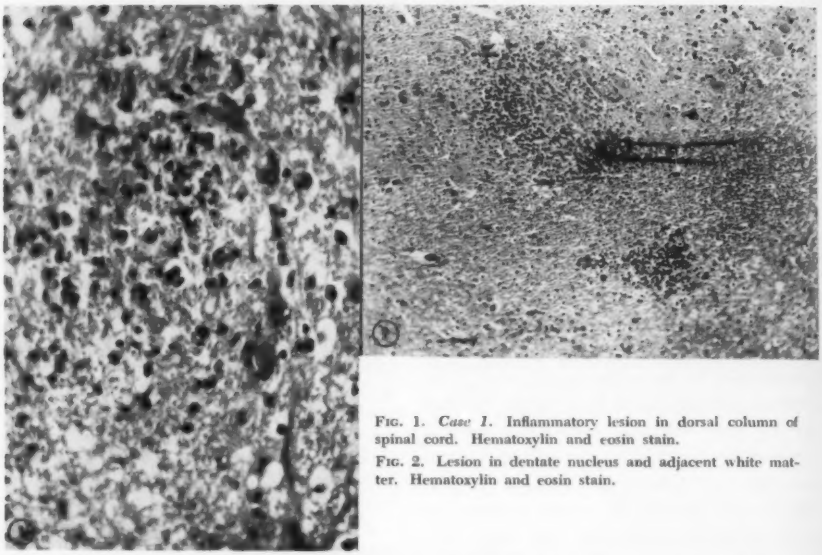

FIG. 1. *Case 1.* Inflammatory lesion in dorsal column of spinal cord. Hematoxylin and eosin stain.

FIG. 2. Lesion in dentate nucleus and adjacent white matter. Hematoxylin and eosin stain.

cent to a lesion in the dentate nucleus (figure 2). This was not in relation to a blood vessel.

*Case 2.* Three weeks before her death a ten and a half year old girl had contact with an individual who subsequently developed poliomyelitis. One week before death the patient experienced fever, sore throat, and anorexia, and four days later pain and rigidity of the neck and vomiting occurred. The voice was slightly hoarse, and the next day she was admitted to the hospital. Two days before death the fever increased to 105° F. and difficulty in speaking and swallowing became apparent, as well as some weakness in the diaphragm and the deltoid muscles. A tracheotomy was performed because of increasing respiratory difficulty and the patient was placed in a respirator. An intermittent shock-like state associated with convulsive movements characterized the last 12 hours of life. There were no clinical observations of sensory loss.

General autopsy revealed visceral congestion and pulmonary edema. The cerebral gyri appeared somewhat flattened, with a concomitant narrowing of the sulci, and the lateral and third ventricles were slightly compressed. The leptomeninges were congested. The tissues of the floor of the fourth ventricle were congested and dusky in hue. The gray matter of the cord revealed a slight yellow tint. Microscopically, a slight lymphocytic infiltration was noted in the leptomeninges of the cord, but not elsewhere. The gray matter of the cord revealed many focal and confluent areas in which collections of polymorphonuclear and phagocytic cells were noted. Many neurons were intact and appeared normal, while others showed chromatolytic changes or cell shrinkage, and a few appeared necrotic. Some of the focal inflammatory collections were the size and shape of neurons and presumably indicated the site of necrotic neurons. Many of the vessels showed numerous lymphocytes and a few phagocytes in the perivascular spaces, and this was true of some of the vessels in the white matter as well. Similar changes were noted throughout the brainstem.

Of special interest was the presence of a single focal lesion in the lateral column of the white matter, characterized by a focal collection of polymorphonuclear and microglial cells (figure 3). This appeared to extend out from the wall of a small blood vessel. The vessel was not thrombosed, but the wall was infiltrated by polymorphonuclear and large mononuclear cells and was probably necrotic.

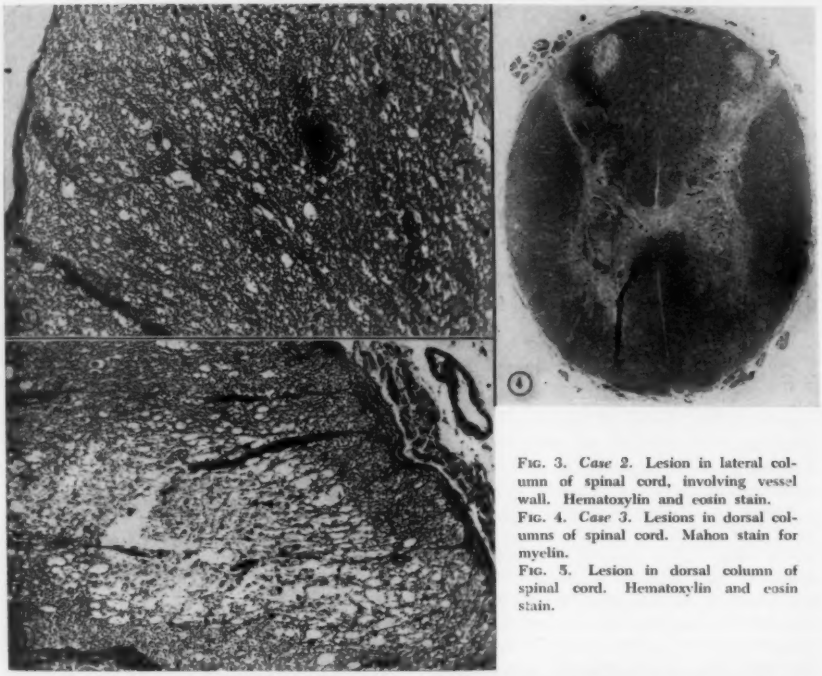

FIG. 3. *Case 2.* Lesion in lateral column of spinal cord, involving vessel wall. Hematoxylin and eosin stain.
FIG. 4. *Case 3.* Lesions in dorsal columns of spinal cord. Mahon stain for myelin.
FIG. 5. Lesion in dorsal column of spinal cord. Hematoxylin and eosin stain.

*Case 3.* A 17 year old boy developed an upper respiratory infection with fever and weakness 12 days after exposure in a poliomyelitis epidemic. The next day, nine days before death, he was admitted to the hospital because of weakness of all extremities, paralysis of the intercostal muscles, and respiratory difficulty. He was placed in a respirator, and subsequently a tracheotomy was performed because of progressive weakness of the musculature of the pharynx and larynx and evidence of involvement of most cranial nerves, including those innervating the extraocular muscles. Death followed a number of episodes of coma. There were no clinical observations indicating sensory loss in the trunk or extremities.

Autopsy revealed an aspiration pneumonia, generalized lymphadenopathy, splenomegaly, fatty infiltration of the liver, and focal myocarditis possibly related to the poliomyelitis virus. The brain was congested but revealed no other gross changes. The gray matter of the cord revealed a marked yellow-brown discoloration at most levels. These tissues were granular and retracted and appeared grossly necrotic. Microscopically, the leptomeninges were infiltrated throughout by small numbers of lymphocytes. There was an almost total destruction of the gray matter at some levels, with a complete loss of all neurons and nearly all neuroglial cells and a marked proliferation of microglial phagocytes. A diffuse lymphocytic infiltration was present, most marked in the perivascular areas. Similar changes of a lesser degree were present in other areas of the cord and throughout the brainstem. These tended to be more focal in distribution. The perivascular lymphocytic infiltration was present in the white matter as well.

Of special interest was the presence of two zones of tissue destruction, each approximately 1 mm. in diameter in the dorsal column just beneath the leptomeninges (figure 4). In these zones, the tissues were rarefied and showed a loss of axons and myelin sheaths and a moderate proliferation of microglial phagocytes,

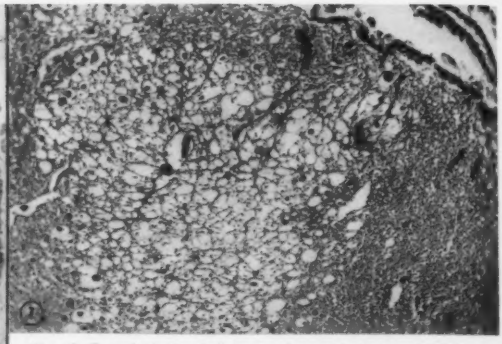

FIG. 6. *Case 4.* Lesion in lateral column of spinal cord. Mahon stain for myelin. FIG. 7. Lesion in lateral column of spinal cord. Hematoxylin and eosin stain.

some of which contained fat (figure 5). Inflammatory changes were not prominent within or about these lesions, nor were vascular alterations noted.

*Case 4.* A 16 year old boy developed slight headache, stiff neck, and backache 17 days before death. The symptoms increased progressively and became associated with fever and weakness in both arms, urinary retention, and difficulty in breathing and swallowing. A tracheotomy was performed and he was placed in a respirator. Death occurred suddenly.

Autopsy revealed a marked dilatation of the right ventricle and subendocardial and myocardial petechial hemorrhages. Petechial hemorrhages were also noted in the subcortical and other portions of the white matter, but were not readily apparent in the cortex and basal gray structures. Petechiae were present in the tegmentum of the rostral medulla. The gray matter of the cord, especially at cervical levels, was hemorrhagic, softened, and friable, while at other levels petechial hemorrhages were seen without marked necrotizing changes. Microscopically, a slight diffuse lymphocytic infiltration of the leptomeninges was noted. Small focal hemorrhages, occasionally perivascular, were present in the subcortical white matter, corpus callosum, and tegmentum of the medulla, and larger hemorrhages were present in the gray matter of the spinal cord. At some levels in this latter tissue, there was a severe loss of neurons and of most other neural elements, with a marked proliferation of microglial cells, most of which appeared phagocytic. At other levels the involvement was less severe and more focal. Perivascular lymphocytic infiltrates were noted in both gray and white matter.

Of special interest was the presence in the thoracic cord of a lesion in a dorsal spinocerebellar tract approximately 1 mm. in diameter, with smaller but similar lesions elsewhere in the lateral column on both sides (figure 6). These lesions consisted of zones of rarefaction, loss of axons and myelin sheaths, marked swelling of some axons, and a minimal proliferation of microglial cells (figure 7). Inflammatory changes were not prominent in these lesions, nor were vascular changes noted.

## DISCUSSION

The most frequent pathologic change in the white matter is the occurrence of perivascular lymphocytic infiltrates. Unless very severe, these probably do not result in an appreciable functional loss.

In the first two cases presented, those of shortest duration, focal areas of acute inflammation were noted in the white matter, characterized by an infiltration by a few polymorphonuclear cells and a more marked proliferation of microglial phagocytes. In some but not all instances, these lesions involved the wall of a blood vessel and showed inflammatory and, in one instance, necrotizing

changes. Capillary thrombosis was observed in one lesion. Although occurring in individuals with severe inflammatory changes in the gray matter and at the same cord levels as these severe changes, the white matter lesions were not generally situated adjacent to the gray matter, but were more often present near the leptomeningeal surface. The leptomeninges overlying these zones showed inflammatory changes no greater than those noted elsewhere. Although lesions were small, it is likely the fibers traversing them would be functionally impaired.

In cases of longer duration, larger lesions of a different character were observed in the white matter. These consisted of areas of marked rarefaction, within which a profound loss of axons and myelin sheaths had occurred. In one instance, markedly swollen and degenerated axons could be distinguished. An astrocytic response was negligible, while the microglial reaction was moderate in one instance and slight in the other. Inflammatory infiltration was minimal. The nature of these lesions is not entirely clear. If the inflammatory reaction had been greater, it would have been apparent that the lesions were due to the direct effect of the virus.

In other viral diseases, such as herpes encephalitis and the equine encephalomyelitides, focal lesions may be seen in which the inflammatory reaction is minimal at some stages. The presence of small numbers of neurons in the white matter[9] may serve as the localizing focus for the virus in this location, although these were not recognized in the cases presented, and their presence need not be postulated since the virus may propagate in other tissues, including those of mesenchymal character. The involvement of blood vessels in the more acute cases suggests an alternative possibility, that these older lesions represent focal areas of atypical ischemic infarction secondary to vascular involvement. There must have been a functional deficit in the fibers traversing these lesions, which were significantly large in size.

It must be emphasized that the lesions in the white matter are certainly of much less significance than the severe lesions in the gray matter. It is not surprising that the functional disturbance relating to the white matter lesions has escaped clinical attention. Recent clinical reports[5] have indicated that sensory changes of a type which might be related to such lesions have been observed, and that these should be included among characteristic clinical features of the disease.

SUMMARY

Lesions in the white matter are described in four cases of acute poliomyelitis. These may be correlated with recent reports of sensory loss in this disease.

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# Effect of Temporal Pole Ablations on Epileptic Tendencies of Monkeys

*Margaret A. Kennard, M.D.*

THE PROBLEM OF EPILEPSY as related to the temporal lobes in man is one about which there has been much recent discussion. Since the discovery by Klüver and Bucy[1] that bilateral ablations of the temporal lobes in monkeys produced a marked change in behavior, much has been published which compares the performance of the human with temporal pole lesions to that of these monkeys. Much is also well known now about the form of epilepsy which appears in individuals who are known to have lesions of the temporal lobes.[2] Lennox[3] now reports that about 20 per cent of his patients with epilepsy have such temporal lobe syndromes and that many of the lesions are bilateral. Feindel and Penfield[2] have discussed the location of "memory" as related to the mesial, older portions of this region, and Bailey, Green, Amador, and Gibbs,[4] among others, have obliterated abnormal paroxysmal behavior patterns by ablations of temporal foci in man.

The present report is part of a study undertaken a number of years ago in which the effect of ablation of frontal and temporal poles on induced epilepsy in the monkey was investigated.[5,6] Prior to this, it had become evident that removal of the frontal poles in man lowered the threshold for motor epilepsy at least temporarily, since about ten per cent of frontal lobotomies performed according to the older technic with the larger lesion were followed by clinical epileptic seizures. The same observation had been made in monkeys following bilateral frontal lobectomy.[6] These animals, previously made epileptic with aluminum hydroxide, became more prone to seizures following bilateral removal of the frontal poles. Since there is ample proof, both anatomic and physiologic, of the interrelationship between frontal and temporal poles, it then became of interest to observe the relationship of ablation of the latter regions to epileptic tendencies. For this reason the behavior of monkeys in the chronic state before and after temporal pole ablations is here reported.

## METHOD

About 30 monkeys (Macaca mulatta) have been observed in this fashion over a period of three years. The procedure

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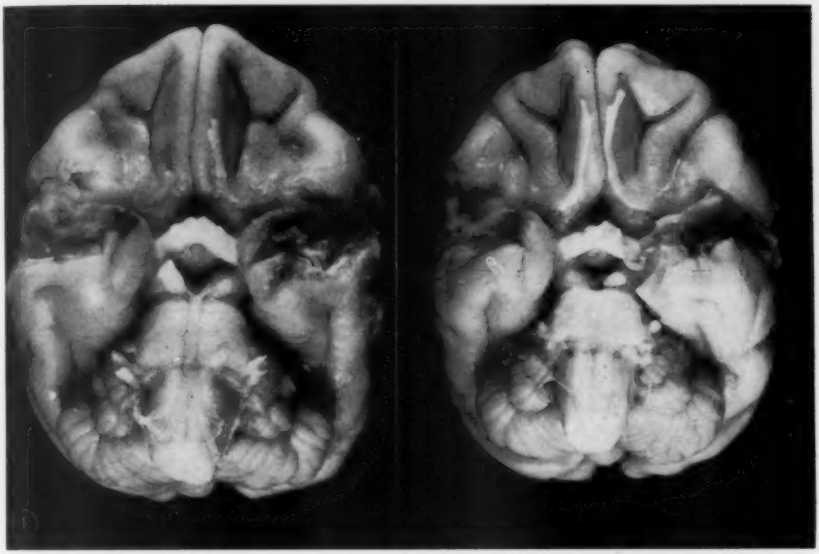


FIG. 1. Brains of two monkeys (Macaca mulatta) showing bilateral temporal pole lesions producing syndrome described in text.

was as follows. All animals were healthy, young, either immature or adult monkeys which had been kept in the colony over a period of several months prior to being inducted into the experimental procedures. These animals had been observed as to type of normal cage behavior and reaction to various stimuli in the cage setting. Electroencephalograms were run in the normal state, at least three satisfactory ones being recorded during this preliminary period. The monkeys were then subjected to cortical operations. At the first operation they were made epileptic either by the placement of aluminum hydroxide on the right motor arm area or a temporal pole was removed. At a second operation some months later the other procedure was carried out. Each animal eventually had three operations – removal of first one and then the other temporal pole and the placement of aluminum hydroxide. Thus, each animal became epileptic and minus both temporal poles.

The exact procedure of operation and of aluminum hydroxide placement has been described in the previous paper related to frontal pole activity.[6] The size and site of ablation of temporal poles are shown in figure 1. All of the temporal pole rostral to the level of the lateral end of the central sulcus was removed. Care was taken to remove all of the mesial portion as well as lateral areas. The temporal horn of the lateral ventricle was opened in most but not all cases. No animal showed hemianopia following operation, so that optic tracts had been left intact. All, after removal of the second temporal pole, showed characteristics of the Klüver syndrome.

The details of electroencephalographic examinations have also been given pre-

viously.[6] Records were made at two-week intervals. Stroboscopic stimulation was used as an index of sensitivity of cortical responses. Since paroxysmal activity appears in all records of normal resting and relaxed monkeys, the amount of this activity was counted over the entire record in each case and the per cent of such activity indicated on graphs.

The myoclonic twitches which accompanied resting or drowsy periods in these animals were also noted during the period of electroencephalographic recording. The method of procedure for this and for all other laboratory details is identical with those used in frontal pole ablations described previously.[6]

DATA

*Seizure Characteristics*

The changes in behavior of the monkey made epileptic at a first operation by focal application of aluminum hydroxide are already well known. In our series, all animals having this application to the motor area showed contralateral focal seizures originating in the hand and appearing within the first two to four weeks following operation. During succeeding weeks, the paroxysmal pattern then gradually became more generalized, appearing first throughout the entire contralateral musculature, and at a later date resulting in generalized grand mal seizures with loss of consciousness. The number of seizures and their duration and severity varied according to the individual animal but was relatively constant for a given animal. All were more susceptible to seizures when anxious or frightened, as when being caught for examination. Once the pattern of seizures was established, it persisted unchanged over the two or three years during which the animals were observed.

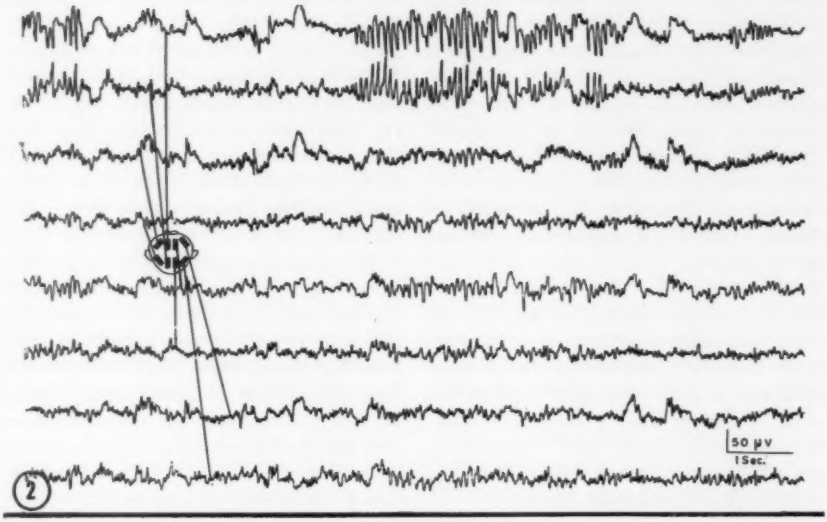
The electroencephalographic pattern recorded during inception of epilepsy and thereafter showed what might be expected, a developing focal paroxysmal area at the site of the lesion, followed later by a generalized increase in paroxysmal tendencies and a marked increase in sensitivity to stroboscopic stimulation.

*Frontal Pole Ablations*

We have reported previously that bilateral ablation of frontal association areas produces a marked change in the electroencephalographic pattern, with indications of increased sensitivity and amount of paroxysmal activity, both with and without additional application of aluminum hydroxide.[7] Such animals present the behavioral syndrome of hyperactivity and easy distractibility well known to be related to the absence of frontal poles in the monkey.[5] In addition, the paroxysmal tendencies of the electroencephalogram were increased in the normal animal following primary frontal pole ablation and markedly augmented in the epileptic animal. The myoclonic twitching of fine musculature which accompanies paroxysmal activity in these animals also became very marked, and the number and severity of clinical seizures increased in those animals chronically having seizures. It should be emphasized here that the character of the motor seizures was not altered in any way by these frontal ablations. The bilateral ablation of temporal poles, in contrast, produced alteration in the nature of the paroxysmal clinical patterning.

*Primary Unilateral Ablation of Temporal Pole*

Primary unilateral ablation of a temporal pole had no effect on cage performance, nor was any to be expected, since previous observations by others



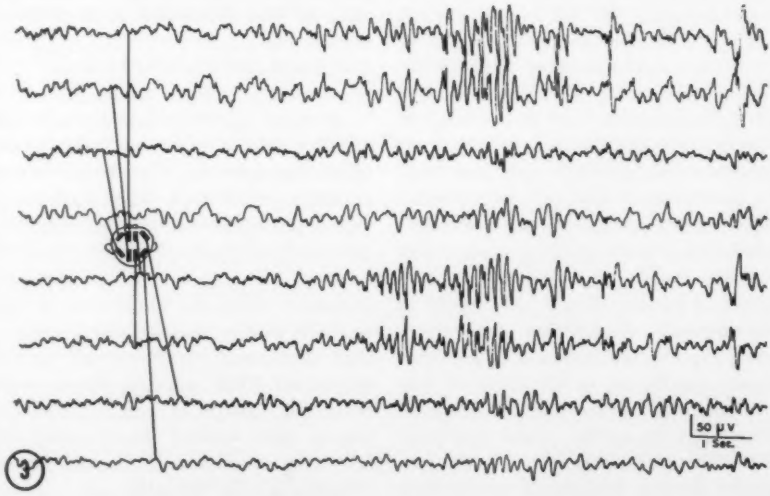




FIG. 2. Electroencephalogram of monkey following unilateral ablation of temporal pole. Note that paroxysmal activity is most marked in frontal regions on right side.

FIG. 3. Electroencephalogram of monkey following bilateral temporal pole ablation. There is bilateral paroxysmal activity throughout all recording area, although most marked in frontal poles.

have never detected marked changes in behavior following removal of one temporal pole. There was, however, a marked change in electroencephalographic pattern. Within the first postoperative week, the site of the lesion developed a high voltage fast activity and paroxysmal pattern (figure 2) which was maintained throughout the duration of the experiment. In addition, the amount of generalized paroxysmal activity increased markedly. The twitching of the fine musculature during paroxysmal periods, probably associated with drowsiness, increased markedly. No clinical epileptic seizure was ever seen, however, following this or any other ablation, unless the cortex had been actively potentiated with aluminum hydroxide.

*Bilateral Temporal Pole Ablation*

Bilateral seriatim removal of temporal poles produced the full-blown clinical syndrome of Klüver and Bucy.[1] In these cases two months or more elapsed between time of removal of first and second temporal poles, and in the interval electroencephalographic and behavioral studies were carried out until such time as a steady state was found to pertain. Following the second operation the animals became quiet, non-aggressive, and apathetic, showing the tendency to nose, smell, and handle all objects brought to their attention. In addition, we noted a special type of performance which later became significant in the light of the performance of these same monkeys when subsequently made epileptic. These bilateral temporal animals frequently showed periods in which they appeared to be listening, or perhaps immobilized for some other reason, with attention turned elsewhere. The attendants to the colony called this "seeing ghosts." A monkey, quiet and apathetic because of his Klüver syndrome, might be watching our procedure from its cage. Rather suddenly it would immobilize, turn its head, usually up and to one side, gaze fixedly, and appear to be listening. It was noteworthy that these episodes became more frequent when the animal was agitated, as when a neighboring animal was to be caught by net.

The electroencephalograms following bilateral temporal ablation showed marked and extreme increase in paroxysmal activity, which was focal to the extent that the patterns were of high and fast voltage over temporal areas (figure 3), but which were also generalized in that the total paroxysmal activity of the record increased greatly (figure 4). Fine muscle twitching and apparent drowsy periods during recording were increased also, as was sensitivity to stroboscopic stimulation.

*Combined Ablation of Temporal Poles with Aluminum Hydroxide*

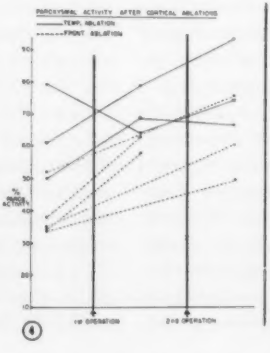
As stated above, all animals were subjected to three operations, with several months between each procedure. Whether the animals were made epileptic at first or last operation, marked changes in the epileptic syndrome resulted from the removal of temporal poles. Cage performance changed. There was a great increase in the number and severity of clinical seizures, and several animals developed focal seizures during which twitching, usually of face or arms, continued over several days immediately following operation (epilepsia partialis continualis). As we also saw following frontal pole ablation, this extreme potentiation of epileptic tendency was always greatest during the first postoperative days and then subsided somewhat, always, however, leaving a state

of increased frequency and severity of seizures when compared to the status preceding ablations.

In addition, these animals all showed alterations in the pattern of their epilepsy which never occurred following frontal ablations. In the case of the temporal ablations many unusual paroxysmal patterns appeared. One animal with epilepsia partialis continualis developed this seizure pattern in the right hand, arm, and face. The aluminum hydroxide had been applied to the right motor arm area, and the motor seizures preceding temporal ablation had always originated in the contralateral left arm and hand. No motor paresis or seizure pattern has, of course, ever been seen following temporal pole ablation by itself.

Two other animals showed excellent facsimiles of psychomotor automatism in their performance which, prior to temporal ablations, had contained purely motor Jacksonian fits. Both of these developed periods in which they sat in unusual positions in their cages and for several minutes were entirely unresponsive to any type of stimulus. One of these, during such a seizure, could be poked with finger or stick and very easily toppled out of the sitting position into a relaxed "faint" on the floor of the cage, from which he recovered within a minute or so, returning to normal cage activity. These animals also had the typical motor generalized seizures which they had had before temporal ablations. It seemed to the observers that all these animals showed more of the "seeing ghosts" behavior described above when they had been subjected to all three operations and were, as a result, both epileptic and without either temporal pole.

The electroencephalographic patterns of the bilateral temporal ablations which were also epileptic were, as might be expected, extraordinarily paroxysmal. Total paroxysmal activity increased markedly. High voltage fast activity appeared almost constant in temporal areas. It was of the kind associated with increased cortical activity and sensitivity, which was borne out by a marked increase in reactivity to stroboscopic stimulation and more frequent development of harmonic patterns during this procedure. The twitching of fine musculature associated with drowsy periods and paroxysmal activity also increased. Figure 4 shows the paroxysmal activity of



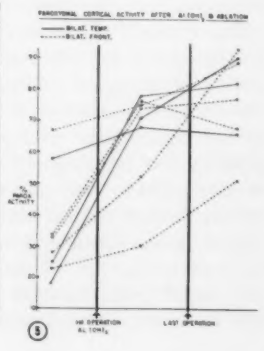




FIG. 4. Paroxysmal activity after cortical ablations, showing increase in all but one case (originally very high) and appearing following either unilateral or bilateral ablations.

FIG. 5. Increases in paroxysmal electroencephalographic activity following administration of aluminum hydroxide to right motor cerebral cortex. There is also some increase in this activity following ablation of either temporal or frontal poles as second procedure following the aluminum hydroxide. Each dot is that of average percentage of three or more recordings at two-week intervals.

several monkeys which had unilateral or bilateral ablations of either frontal or temporal association areas. It will be seen that paroxysmal activity increased in every case but one. Since the bilateral frontal ablations discussed in the previous paper were performed at one operation, the effect of this can only be shown at the end of the bilateral removal. For this reason, after it was found that unilateral removal of temporal poles caused increased paroxysmal activity, a single frontal pole was removed in two instances, as shown in figure 4. In each case there was a significant increase in paroxysmal activity. With the temporal ablations the total effect after bilateral ablation was an increase in paroxysmal activity, except in one instance in which the original count was unusually high. In each case the level of paroxysmal activity, shown in figure 4 as a percentage, was the average of three or more counts of such activity, records being made at two-week intervals.

Figure 5 shows a similar but more marked rise in total paroxysmal activity appearing in eight other animals following administration of aluminum hydroxide at a first operation and the appearance of clinical seizures. The effects of subsequent operations, which were either bilateral simultaneous removal of frontal poles or bilateral seriatim removal of temporal poles, produced a further rise in paroxysmal activity in six of the eight cases. Changes here were possibly less significant than in figure 4 because these were averages of more widely variant counts. As would be expected in an epileptic animal, as in man, the total excitability of the epileptic cortex varied greatly and in proportion to the status as related to previous or imminent clinical seizures.

*Stroboscopic Stimulation*

Stroboscopic stimulation was used during each electroencephalographic recording. A fixed pattern of stimulation was used, in which the animals were subjected to flicker rates ranging from four to 12 per second for fixed intervals and at a fixed light intensity. Changes which occurred were shown to be those indicating increased sensitivity, either a lowered threshold for alteration in frequency pattern as shown on frequency analyser records, or an increased tendency to develop clinical seizures. When the reverse occurred, the cortex was considered to have become less sensitive. Following either frontal or temporal ablations, increased sensitivity usually appeared and was marked after the bilateral ablations. In those animals made epileptic with aluminum hydroxide, the incidence of seizures induced by stroboscope flicker was proportional to the degree of epileptic activity of the animal. It was also found to correspond to the amount of paroxysmal activity appearing during normal rest and to changes in relation to such activity. There was one exception to the above, namely that during periods in which epileptic animals were showing extreme cortical sensitivity, as shown by the number of clinical seizures and by the unstimulated resting paroxysmal activity, the cortex became, in many instances, either relatively or completely resistant to stroboscopic stimulation. It seemed then as though the strong stimulus pattern of the epileptic focus evoking paroxysmal cortical activity was sufficient to prevent the effects of the stroboscope. This finding is unexpected, since at other times the stimulus sent by the flicker could, in the same monkey and at the

same frequency, induce a clinical seizure. When this happened, however, the resting record was always less "paroxysmal" than in those animals more prone to spontaneous seizures whose electroencephalographic patterns were already extremely paroxysmal.

One other finding which was unexpected should be reported here. The frequencies used for flicker stimulation were always the same and were those slower, equal to, or faster than the basic "alpha" rate of the macaque, which is around five to six per second. There was never any single rate which appeared to be that to which the patterns were most responsive. Rather, the entire series of frequencies would appear to be either more or less productive of response according to the immediate cortical sensitivity.

*Removal of All Four Association Areas*

Following either bilateral frontal or temporal ablations, the remaining association areas were also removed in four animals. All these animals were also epileptic from aluminum hydroxide. The findings ultimately were the same, irrespective of the sequence of operative procedures. These animals remained epileptic and markedly sensitive to all sorts of epileptogenic stimuli, such as fear or the stroboscope. Their electroencephalographic patterns reflected this hypersensitivity. Their cage behavior changed markedly. Although all could carry out ordinary cage procedures such as feeding themselves, they became totally unable to cope with other animals in the same cage. They were at once hyperactive and perseverative in movement, repeating motor activity, as has been described as an effect of frontal ablations.[5,8] But they were also far less motile when left alone and would sit motionless unless disturbed. Automatic motions, "ghost seeing," and a tendency to repeat movements relating to the handling, tasting, or smelling of objects continued. They did not appear afraid to the degree usually seen in normal animals, but continued to develop seizures in anxiety-provoking situations. They appeared confused and far less in contact with their surroundings than they had prior to the removal of all association areas.

## DISCUSSION

The findings here reported are consistent with those of our previous paper, which dealt with the effects of frontal pole ablation.[5] It appears that either frontal or temporal association areas, while actively functioning, have some limiting and regulating effect on cortical activity and, by this means, upon total behavior. When this effect is either distorted or removed by structural changes, the type of change is one of increased total activity, one element of which appears to be paroxysmal. The fact that similar dyscoordination occurs following removal of either frontal or temporal association areas is of interest in relation to the relatively late development of the newer portions of these areas.

There is evidence here of some recoordination and re-assembly of normal cortical function during the postoperative periods, since many animals showed far greater incidence of clinical seizures immediately following operation than later, when they had far fewer seizures. This tendency to fewer and fewer seizures was maintained throughout the two- to three-year period in which we observed these animals. At the end of the first year, for instance, many animals had only one or two seizures during the en-

suing six months, although they had had many more during the first year following operation. This is, of course, well known to be the case with man, in whom a few seizures following cortical ablations such as that of frontal or temporal pole may occur postoperatively, although there are none following this period.

It is of interest here that temporal pole ablation always produces so much generalized effect on both the cortical potentials and the behavioral qualities. In this respect, its effect appears much more widespread than that of frontal poles (areas 9-12 of Brodmann). In the latter case, all of the changes which occur following ablation can be related to motor status, and there is a motor effect of this procedure on the motor seizures caused by aluminum hydroxide. In contrast, the effects of temporal pole ablation are always generalized and affect total behavior. Additional paroxysmal behavior changes definitely appear when temporal ablation is added to aluminum hydroxide. Thus, both temporal and frontal ablations increase tendency to motor seizures, and both modify general behavior in a particular way which is constant. In addition, temporal ablation in the presence of epilepsy causes generalized paroxysmal behavior, although no paroxysmal behavioral pattern except the motor seizures follows frontal procedures. The modification of motor pattern described above following temporal lesions has never been seen after frontal ones.

Since the mesial archicortex of the temporal pole was removed as well as the lateral cortex in every instance during the present series, there is no indication here as to the separate effects of the two developmentally different regions. It would be expected that the older cortical regions would have more generalized and behavioral effects than the more recent areas. This might then account for the difference between frontal and temporal effects as described above. The cingulate area, the "older" frontal region, has not yet been studied in relation to these seizure patterns.

Finally, the similarities between the effects of these lesions on man and on the monkey are perhaps instructive. Those which follow frontal ablations are already well known. Increased epileptic tendencies, as shown in the electroencephalogram and in clinical seizures following frontal pole ablation, have already been noted. The appearance of these tendencies has been related to preoperative paroxysmal tendencies in both man and monkey also. Although motor epileptic tendencies are thus increased, no other paroxysmal behavioral change has ever been reported as the result of frontal pole ablations. The changes in behavior and in relation to environment which appear in both man and monkey after either frontal pole ablation or injury to the mesial frontal areas (area 24 of the archicortex, the cingulate gyrus) are, in contrast, relatively steady rather than paroxysmal.

Changes in behavior following temporal association damage are likewise similar in man and monkey. Unilateral injury causes increased cortical sensitivity, as indicated by paroxysmal bursts and spike activity in either instance. Paroxysmal behavior follows in man, but has not yet been noted in the monkey. After bilateral ablation, either man or monkey may show a change in total pattern of behavior and also a great increase in paroxysmal activity, both at an electroencephalographic and at a behavioral level. The character of the par-

oxysmal activity has always an element of automatism and of dissociation with immediate environment, such as "ghost seeing." Paroxysmal aggressive bursts are described in man, but have never been seen in the monkey.

We have recently had the opportunity to examine a patient who has had bilateral temporal pole ablations and who shows many of these characteristics. This patient, a 44 year old man, sustained an injury to the right side of his head in 1944; he developed violent aggressive behavior and paroxysmal automatism. A spike focus was found in the right anterior temporal region, following which he had an ablation of this region. Two years later, since his behavior was unchanged, the left temporal pole was also removed at operation. There was again no change in behavior. He has been for some years committed to a mental hospital where he is reported to have many brief seizures of automatism daily and to show clouded, confused, and belligerent behavior frequently. He is markedly paranoid and his memory for time and place is poor. He consistently denies any knowledge of his automatism. These seizures consist often of a few seconds of abrupt and violent arm movement, turning of the body to the right, and a cry which sounds angry. Objects may be knocked over during this episode, and his hand movement appears directed to hit out at an intervening object or person. Other types of seizure have also been described. His electroencephalic pattern is very similar to that seen in the monkeys following temporal pole ablations. In each temporal area there are very high voltage, fast and irregular wave forms such as those shown in figures 2 and 3. In addition, there are frequent spike potentials in the right anterior temporal region. Neurologic examination between seizures is normal. It seems very likely that this case presents evidence of bilateral increase in paroxysmal tendencies which is the result of the removal of temporal poles and which, in this instance, as in that of the monkeys here described, has been superimposed upon an epileptic tendency. In the light of other case reports elsewhere, it is probably indicative of the mechanism which underlies the many failures to abolish temporal pole epilepsy in man by ablations. If these observations are correct, then the increased tendency to epilepsy which follows these relatively small lesions should be taken into consideration in all operations upon temporal poles. Since it is also known that severe and undesirable effects follow larger removals, particularly upon the dominant hemisphere, localization for ablation within the temporal area must require great accuracy.

## CONCLUSIONS

1. Unilateral or bilateral removal of temporal association areas in the monkey is followed by an increase in epileptic paroxysmal tendencies as shown by electroencephalographic pattern and by clinical seizures.

2. The increase in motor seizures in epileptic monkeys, in myoclonic twitching, and in generalized paroxysmal activity are all similar to those which follow ablations of the frontal poles.

3. In addition, ablation of temporal poles adds a paroxysmal behavioral quality to the Klüver and Bucy syndrome.

4. The paroxysmal activity of the temporal ablation involves total behavior and blunting or alteration in response to environmental stimuli.

5. In the absence of both frontal and temporal association areas, the paroxysmal confusional syndrome of the monkeys becomes augmented.

6. The similarities of these behavioral patterns in monkeys to those which appear in many humans following lesions of association areas are discussed, with particular reference to one patient having bilateral temporal pole ablations.

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■ Almost all modern writers on epilepsy mention worms among its most common causes. — Van Swieten observes, that by creeping in the intestines and stomach, they irritate and hurt those parts, and frequently produce the disease; and he relates the case of a boy, two years of age, of a good constitution, who died of violent and continued convulsions, in whom the duodenum was found perforated by a round worm, which was taken alive out of the body. Numerous accounts of epilepsy arising from this cause may be found in Bartholinus, Stahl, Heister and Wepffer. This last author mentions the case of a girl, three years old, who for several months had been epileptic, and in constant pain, who was cured by spontaneously voiding a large tape worm; and of another, who at the age of seven became cataleptic for three years, and afterwards epileptic, with such frequent paroxysms as to occasion a total imbecility and absolute loss of memory, who, on voiding a single worm, was restored to perfect health, and the enjoyment of all her faculties. — I have seen some cases of epilepsy, in which the disease has ceased on the discharge of worms; and others in which it appeared to have been cured by anthelmintics, although no worms could be discovered in the evacuations.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

# Metachromatic Form of Diffuse Cerebral Sclerosis

## I. Diagnosis During Life by Urine Sediment Examination

*James H. Austin, M.D.*

IN THE PAST THREE YEARS five children with a progressive demyelinating disease of the central nervous system have been investigated in three different families. This disorder is described as the metachromatic form of diffuse cerebral sclerosis (metachromatic leucoencephalopathy). The scope of the present report will be largely limited to a description of the distinctive findings which all five patients have had on urine sediment examination. These reflect directly the pathologic changes found in the kidneys in this disorder.[1] These urine findings, properly interpreted, have permitted a diagnosis of this demyelinating disease of the central nervous system for the first time during life.

A brief and introductory review of this disorder and of this case material is pertinent here. Clinical, pathologic, control, and other details on these patients are discussed in other communications.

In 1910 Alzheimer and Nissl first commented upon metachromatic staining in the central nervous system in a case of diffuse sclerosis.[2,3] Since then, some 18 cases have been reported, only two of them from this continent.[4,5] In this form of the disorder, admixed with the expected diffuse demyelination, gliosis, and axonal loss, are quantities of unusual abnormal materials. These materials occur in granular clumps which stain shades of red with blue basic aniline dyes. They stain a color other than that of the dye used, that is, metachromatically. Accordingly, this form of diffuse sclerosis is known as the metachromatic form. A discussion of the general topic of diffuse sclerosis is given elsewhere.[6,7] These granular structures characteristically do not stain for neutral fats to any degree. This is a significant difference from the neutral fats found in some other forms of diffuse sclerosis and from that usually expected as a reflection of severe loss of myelin. The sum of many histochemical observations has suggested that this material is a mixture of complex glycolipids, probably attached to protein.[4,8,9] Where the metachromatic materials belong in the sequence of the pathogenesis of this diffuse demyelinating disorder is still under investigation.

In four of the five cases in the literature in which it was correctly looked for,

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This study was begun on two patients studied in the child neurology service of the Neurological Institute, Columbia-Presbyterian Medical Center, New York City. It was supported following this by Public Health Training Grant 2-B-5025.

metachromatic materials were also found in organs outside the nervous system.[9–11] Of particular interest to this present report were the deposits described in cells of the kidney tubules. A full description of these deposits in the convoluted, looped, and collecting tubules of the kidney will be presented in a separate communication.[1] These are clearly the source of the abnormal material in the urine sediment. A photomicrograph of a section obtained at kidney biopsy (case T.M.) shows the general nature of the abnormal material (figure 1). This material is not found in either normal or abnormal controls and appears to be specific for this disorder.

The salient neurologic features reported are those of a slowly progressive illness, with quadraparesis and bulbar paresis, extensor plantar responses, and dementia, usually affecting children or young adults. Optic atrophy, strabismus, and incoordination may be superimposed. The duration of illness has been somewhat variable. The shortest is over six weeks and the longest 22 years. Other members in the family in the same generation have been affected in only four reported cases.

The case material of this report (plus their two other affected, autopsied relatives) is more homogeneous. This permits their being discussed here as a group. All are children with an average age of onset of two and one-half years. Five of the seven are males. The disorder is clearly familial, and all have at least one other member of the family affected in the same generation. Each began with an impairment in locomotion and then had a clear-cut progressive disease ending in quadriplegia, with pyramidal tract signs, dementia, and usually optic atrophy. Short generalized seizures are occasionally present in six cases. Spinal fluid protein is moderately elevated. The duration of illness before death has varied from one, to two, to five years. Histologic proof of the disease is present in four of the seven and in each of the three families.

Brief identifying data follow on the five cases examined during life. The means by which the urine sediment diagnosis of the metachromatic form of diffuse sclerosis is supported pathologically is indicated.

*C. Family*

1. T.C. Onset 17 months and death at age six and a half years. Autopsy central nervous system.
   - One affected brother (D.C.) had an onset at 19 months and died at age three and a half years. Autopsy including central nervous system.
   - One other affected brother (J.C.) is still living at age five.
2. J.C. Onset 12 months; still living at age five.
   - Two other affected brothers were autopsied (T.C. and D.C.).

*T. Family*

3. W.T. Onset age five; still living at age nine.
   - One affected cousin (B.W.) with an onset age three died at age three and a half. Autopsy including centra. nervous system.

*M. Family*

4. T.M. Onset age eight months; still living at age six and a half. Renal biopsy at age five and a half positive for the distinctive findings of this disorder (figure 1).
   - One sister (C.M.) similarly affected.
5. C.M. Onset age one and a half years; still living at age eight.
   - One brother (T.M.) had a positive renal biopsy.

## PROCEDURE

The method of urine sediment diagnosis is based on two principles: first, that the abnormal material in the urine may be separated and concentrated by

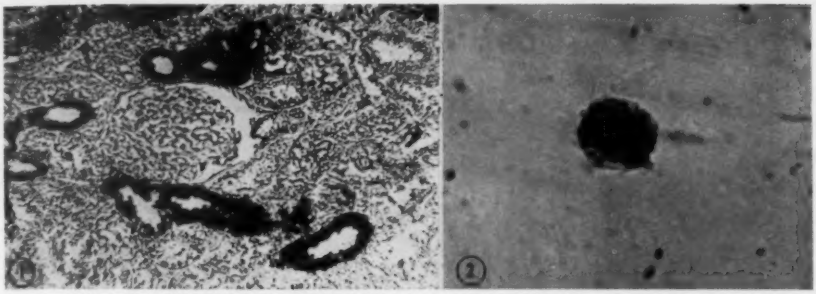


FIG. 1. *Case T.M.* Kidney biopsy. Frozen section stained with toluidine blue O. Proximal convoluted tubule cells filled with metachromatic material (dark). An intact glomerulus is also shown. Control kidneys do not show this staining.

FIG. 2. *Case T.M.* A large granular body stained with toluidine blue O measuring 18 micra in greatest diameter.

centrifuge; second, that it may then be distinctively stained by certain aniline dyes. The use of fresh, clean urine is essential. It should preferably not be infected, contaminated, or contain debris which will obscure the findings. A turbid urate excess may be dissolved by gentle warming. The container is shaken to disperse the sediment. A 10 cc. cone-tipped centrifuge tube of urine is centrifuged in an ordinary clinical centrifuge for five to ten minutes. The supernatant is decanted. One or two drops of a 2 per cent aqueous solution of toluidine blue O is added to the residue and stirred, and two large drops are transferred to a glass slide. Two cover slips are added and the preparation is allowed to settle for one or two minutes. A complete, systematic examination of each slip is then made promptly under high dry magnification. A tungsten source of white light without glare is used. To prevent drying, the edges of the slip may be sealed with petroleum jelly.

## RESULTS

### *Structure*

Abnormal material occurs in several forms and sizes, each basically composed of granules or globules. Six descriptive forms may be recognized. Each patient has had all forms.

*Large oval granular bodies (figure 2).* These are the largest and most characteristic when present (15 to 25 micra in length). They are more frequent in later stages of the disease. Most are similar in general appearance both to the oval granular structures seen in formalin-fixed sections of renal collecting tubules and to those in cerebral white matter. They are for this reason described as "urine granular bodies." They may be somewhat asymmetric and may have irregular outlines. Some are aggregates of more rounded, globular units, each less dense centrally. The appearance of these is somewhat similar to a mulberry or large cluster of grapes. No cell nuclei are seen next to these bodies to suggest that they are now phagocytized.

*Small clusters (figure 3).* These are smaller than the previous bodies (10 to 15 micra) and more irregular in outline. Their individual units may be more clearly globular when seen in fresh urine and the final structure resembles a small cluster of grapes. There are intermediate sizes between small clusters and the

larger bodies. The distinction is useful chiefly for diagnosis in the early case; the smaller forms may not be as conspicuous, but predominate in earlier stages when larger bodies may be lacking.

*Mixed granular bodies.* These are small to medium-sized granular bodies which are composed both of metachromatic globules or granules and of similarly shaped units which do not stain. Both are doubly refractile in polarized light.

*Free granules (figure 4).* These lie scattered like sand throughout the field. They measure 3 to 5 micra in diameter. They also become larger and more frequent in later phases.

*Enclosed granules (figure 5).* Similarly staining collections of granules occur less frequently both in the cytoplasm of renal tubular epithelial cells and inside hyaline casts. These clearly indicate their origin in the kidney.

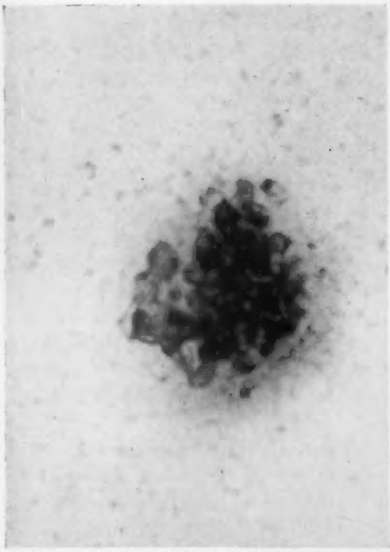
*Casts (figure 6).* Granular material, staining typically, sometimes forms a complete typical cast much longer than it is wide (for example, 6 micra wide, 30 micra long). Some casts are narrow enough to have originated in the loop of Henle. The width of others indicates their origin in larger tubules. These are not to be confused with more homogeneous hyaline casts, which may also be present and which show a pink or violet metachromasia. The latter structures are also found in many other disease states and are in themselves nonspecific.

### *Color*

The unstained sediment is not revealing when viewed in the perspective of the control series. The stained sediment is quite different. Various blue aniline dyes stain the abnormal material different colors. By the time a slide preparation is first seen, the granular, globular material stains a distinct golden-brown with toluidine blue, reddish with methylene blue, and yellow-orange with thionine. An initial more red tinge may be seen to precede these colors but usually fades in a matter of minutes to the more stable colors above. (The red color of material in the kidneys and brain also fades rapidly. The color of that in the kidneys fades to the same golden-brown as do the granular structures in the urine.) Many of the structures rapidly lose their staining identity even when slides are sealed and preserved on ice. The rate of fading of both red-purple and golden-brown colors is greatly increased when the structures are placed in an electrical current. Sediment suspended in 10 per cent formalin, mounted, and sealed has retained its golden-brown color for over a year to date. Exceptionally, granular bodies have persisted in unpreserved sealed slides over three years old. Colors become more dense in later stages of the disease.

### *Refraction Characteristics*

Under polarized light all forms of the urinary granular material are doubly refractile. This anisotropism varies in amount and is faint when compared to that of the usual crystals in urine sediment. It takes the form of small multicolored dots distributed throughout the material (figure 7). The light from some is the same color as that of the stain. The light from others is not. This suggests that the portion of the complex which is metachromatic is not necessarily the same as that which is doubly refractile. In the unstained sediment, the bodies are also doubly refractile. A typical Maltese cross effect (associated with some lipids) is occasionally seen.



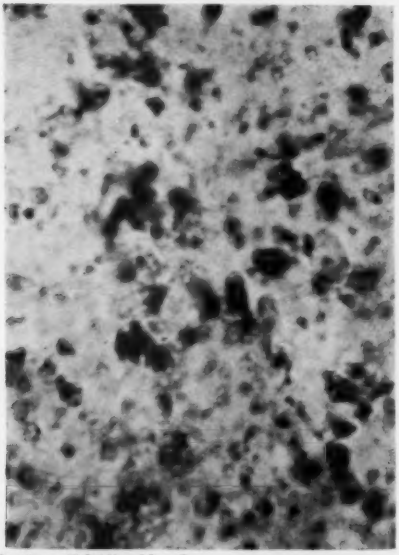


FIG. 3. *(left) Case W.T.* A small cluster measuring 10 micra. Toluidine blue O.
FIG. 4. *(right) Case C.M.* Many free metachromatic granules in an advanced case. Toluidine blue O. Much of what appears to be sand-like debris is actually golden-brown in color.

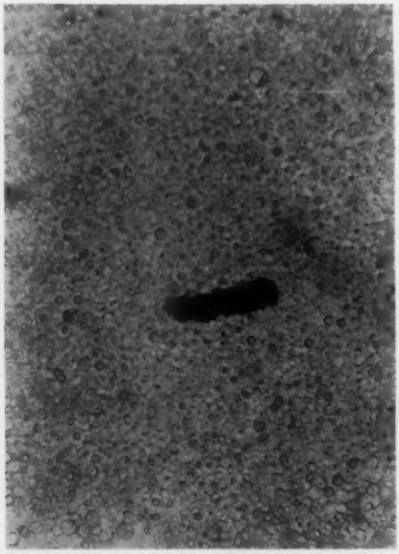


FIG. 5. *(left) Case W.T.* Two renal tubule cells stuffed with intracytoplasmic metachromatic material. Toluidine blue O.
FIG. 6. *(right) Case T.C.* Metachromatic cast 18 micra by 6 micra. Thionine. Round structures are yeast artifacts.

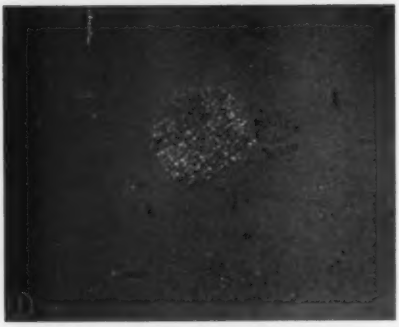


FIG. 7. *Case T.M.* Polarized light. Large granular body 21 micra in diameter. Toluidine blue O.

*Solubility Characteristics*

Typical stainable material is no longer present after extraction of the sediment with an equal volume of chloroform-methanol (2:1) or petroleum ether. Acetone extraction does not remove the stainable material.

*Electrical Charge*

Migration characteristics of granular bodies in an electrical field were studied in two cases. The bodies were stained with toluidine blue, washed with distilled water, resuspended in a potassium phosphate buffer at pH 12, and observed microscopically in a blood counting chamber. A copper electrode was placed in the trough at each end of the chamber and there immersed in the buffered electrolyte solution. One electrode served as the anode (+), the other as the cathode (−). Current source was a Spinco duostat set at 0–200 volts and at a meter range of x 30 volts.

With the current on, when not stuck to the glass, the bodies moved repeatedly toward the positive pole. These preliminary observations are consistent with a net over-all negative charge at this pH.

*Quantitative Aspects*

Some daily fluctuations occur in the number of granular bodies excreted. Followed serially over a period of months, however, their excretion directly parallels the progressive clinical decline of the patient. As each patient worsens, larger, more dense, and more numerous metachromatic structures are excreted. Of two affected siblings, the more advanced sibling will have more abnormal material. These observations carry the important implication that it is possible to have laboratory measurement of the clinical course of this disease.

All patients have been at an advanced stage of the disease when first seen. In an early, ambulatory patient it might be difficult to make a diagnosis without an extensive search of the urine sediment to find the first evidences of the abnormal material. In late stages as many as four to five large granular bodies may be seen in one high-power field. In the one patient in which it was tried, external massage in the flanks over the kidneys for five minutes may have caused an increase in the number of free sand-like granules excreted in subsequent hours.

*Staining Considerations*

The metachromatic staining of the abnormal material by the blue basic aniline dyes, toluidine blue O, methylene blue, and thionine clearly indicates the special properties of these dyes. The blue of commercial blue ink, for example, is ineffective. It is important to appreciate that many different biologic substances may give a metachromatic color when stained with these dyes. The complex substrate-dye interactions which lead to this curious color change have

been investigated at length and are reported in adequate detail elsewhere.[12,13] It is also worth emphasizing that materials staining metachromatically do have some more straightforward common denominators. They are relatively high molecular weight polymerized compounds rich in free acid groups, and thereby negatively charged. Preliminary observations of these granular bodies in an electrical field would tend to support this generalization.

Special pH precautions are not essential in actual performance of fresh urine sediment examination. Two different lots of each dye have been tested. They varied widely in age, degree of contamination, and in the room temperatures and final concentrations at time of use. All were National Aniline dye products. Despite known heterogeneity of these dyes, results in practice are reproducible enough for laboratory diagnosis.

Toluidine blue O has the advantage of being a universal basis for comparison. It has the disadvantage of clumping together the unstructured urinary mucoproteins and obscuring some abnormal golden-brown granular material in its dense meshwork. Methylene blue is an improvement in this respect and still provides a red color of some differential value.

It seemed of interest that a different color for each dye was finally produced after the dye came in contact with the abnormal granular material. Possible mechanisms of this were directly investigated in visible light, which is the condition under which the color problem presents itself to the eye microscopically. In the test tube, at the interface between a dilute unbuffered solution of dye and a strong base like sodium hydroxide (defined here as a proton, $H^+$ acceptor), it was found that the same colors, yellow-orange (thionine), red (methylene blue), and golden-brown (toluidine blue) could be developed. The latter color is more evident microscopically when the partially altered dye which has not been completely decolorized is allowed to spread out. Contact with an acid (proton donor) or an oxidizing agent (20 per cent $H_2O_2$), however, did not change the dye color. The reducing agent sodium hydrosulfite (buffered or unbuffered) rapidly made the dyes colorless without an evident intermediate stage. The preceding preliminary observations suggest the possibility that these particular colors occur because these dyes themselves are changed at this pH in contact with material which is a proton ($H^+$) acceptor. This is also consistent with the concept that the abnormal material is negatively charged from its free acid groups (for example, sulphate, phosphate, carboxylic groups).

These dyes also have oxidation-reduction potentials. The possibility that the final golden-brown color was due to this effect on the granular material itself was tested for in a simple system. Neither the addition of the reducing agent, concentrated sodium hydrosulfite, nor of the oxidizing agent, 10 per cent $H_2O_2$, colored the unstained granular material.

*Other Dyes*

The dyes above afford a color contrast which helps identify the granular material. The following dyes, however, have not provided a useful differential stain for the structures as they exist with many other materials in urine sediment: 5 per cent aqueous phloxine, 2 per cent light green, 2 per cent fast green, 3 per cent methyl green. Three per cent nile blue 9 stains the structures (and other

TABLE 1

CONTROL STUDIES, METACHROMATIC LEUKOENCEPHALOPATHY — 110 CASES

| *Patient* | *Age* | *Diagnosis* | *Granular Bodies* |
|---|---|---|---|
| | | UNAFFECTED MEMBERS OF FAMILY | |
| W.C. | 11 | Brother patients | 0 |
| H.C. | 37 | Father patients | 0 |
| M.C. | 36 | Mother patients | 0 |
| F.M. | 32 | Mother patients | 0 |
| H.M. | 40 | Father patients | 0 |
| B.M. | 11 | Half brother patients | 0 |
| S.M. | 14 | Half sister patients | 0 |
| F.T. | 39 | Father patient | 0 |
| E.T. | 38 | Mother patient | 0 |
| F.T. | 9 | Brother patient | 0 |
| M.T. | 12 | Sister patient | 0 |
| G.T. | 4 | Sister patient | 0 |
| J.T. | 6 | Brother patient | 0 |
| L.T. | 3 | Sister patient | 0 |
| | | CENTRAL DEMYELINATING DISEASE | |
| F.K. | 24 | Acute multiple sclerosis; paraplegia | 0 |
| E.H. | 18 | Multiple sclerosis | 0 |
| R.G. | 49 | Acute transverse myelitis | 0 |
| D.C. | 26 | Active multiple sclerosis | 0 |
| J.D. | 43 | Acute multiple sclerosis | 0 |
| W.P. | 47 | Multiple sclerosis | 0 |
| | | ENCEPHALOMALACIA | |
| S.K. | 56 | Left carotid thrombosis | 0 |
| E.W. | 80 | Left carotid thrombosis | 0 |
| M.N. | 3 | Encephalomalacia after cardiac arrest | 0 |
| R.B. | 2 | Hypoglycemic and post ictal encephalopathy | 0 |
| J.J. | 4 | Encephalomalacia after cardiac arrest | 0 |
| E.B. | 47 | Hypertensive encephalopathy | 0 |
| P.H. | 58 days | Severe anoxia at birth | 0 |
| R.C. | 8 | Decerebrate after anesthesia | 0 |
| | | Decerebrate for one month | 0 |
| | | NEUROPATHY | |
| B.K. | 23 | Charcot-Marie-Tooth | 0 |
| H.M. | 36 | Post infective polyneuropathy | 0 |
| J.F. | 42 | Multiple, asymmetrical radiculoneuropathy | 0 |
| E.F. | 50 | Bilateral radial palsy | 0 |
| A.S. | 45 | Polyneuropathy ? cause | 0 |
| F.C. | 17 | Generalized neurofibromatosis | 0 |
| E.L. | 36 | Charcot-Marie-Tooth | 0 |
| M.W. | 47 | Generalized neurofibromatosis | 0 |
| | | HEREDO-DEGENERATIVE | |
| S.S. | 59 | Alzheimer's disease | 0 |
| C.S. | 25 | Progressive spinal muscular atrophy | 0 |
| W.M. | 3 | Progressive spinal muscular atrophy | 0 |
| M.J. | 61 | Parenchymatous cerebellar degeneration | 0 |
| R.G. | 1 | Tay Sach's disease | 0 |
| C.L. | 26 | Friedreich's variant | 0 |
| W.B. | 58 | Alzheimer's disease | 0 |
| F.A. | 25 | Familial myoclonus epilepsy | 0 |
| O.L. | 61 | Parkinsonism with cerebral atrophy | 0 |
| G.G. | 13 | Hepatolenticular degeneration | 0 |
| J.M. | 6 | ? Diffuse sclerosis | 0 |
| A.D. | 12 | Diffuse sclerosis | 0 |
| R.C. | 15 | ? Pelizaeus Merzbacher's form of diffuse sclerosis | 0 |
| M.R. | 6 | ? Heller's dementia | 0 |
| L.E. | 3 | ? Diffuse sclerosis | 0 |
| J.A. | 11 | Gargoylism | 0 |
| G.C. | 10 | Gargoylism | 0 |
| M.V.D. | 5 | ? Amaurotic family idiocy | 0 |
| S.E. | 5 | Diffuse sclerosis | 0 |
| T.E. | 3 | Diffuse sclerosis | 0 |

TABLE 2

CONTROL STUDIES, METACHROMATIC LEUKOENCEPHALOPATHY — 110 CASES

| *Patient* | *Age* | *Diagnosis* | *Granular Bodies* |
|---|---|---|---|
| | | RENAL | |
| J.R. | 6 | Nephrosis | 0 |
| S.S. | 2 | Nephrosis | 0 |
| A.V. | 70 | Chronic glomerulonephritis; uremia | 0 |
| C.T. | 56 | Chronic glomerulonephritis; uremia | 0 |
| R.T. | 24 | Acute glomerulonephritis | 0 |
| V.C. | 11 | Acute glomerulonephritis | 0 |
| S.P. | 12 | Lupus erythematosus | 0 |
| M.E. | 60 | Multiple myeloma | 0 |
| G.D. | 58 | Multiple myeloma | 0 |
| A.E. | 58 | Pyelonephritis, metastatic carcinoma | 0 |
| I.M. | 77 | Pyelonephritis | 0 |
| R.R. | 54 | Cardiac decompensation | 0 |
| | | HEPATIC | |
| N.C. | 23 | Hemolytic and obstructive jaundice | 0 |
| J.S. | 62 | Obstructive jaundice | 0 |
| M.C. | 53 | Cirrhosis with jaundice | 0 |
| G.K. | 61 | Metastatic carcinoma to liver with jaundice | 0 |
| G.P. | 28 | Infectious hepatitis with jaundice | 0 |
| F.H. | 14 | Infectious hepatitis with jaundice | 0 |
| W.P. | 46 | Portal cirrhosis with jaundice | 0 |
| H.D. | 19 | Chronic hepatitis | 0 |
| | | MUSCULAR | |
| M.R. | 4 | Muscular dystrophy | 0 |
| H.H. | 48 | Myotonic dystrophy | 0 |
| K.A. | 43 | Muscular dystrophy | 0 |
| L.K. | 34 | Myositis | 0 |
| M.C. | 42 | Dermatomyositis | 0 |
| | | MISCELLANEOUS | |
| A.T. | 9 | Acute cerebellar ataxia, ? etiology | 0 |
| J.M. | 40 | Wegner's granulomatosis | 0 |
| B.Y. | 5 | Encephalopathy ? etiology | 0 |
| P.K. | 51 | Pinealoma | 0 |
| S.L. | 2 | Encephalopathy ? etiology | 0 |
| C.C. | 34 | Normal | 0 |
| J.A. | 28 | Normal | 0 |
| A.A. | 70 | Metastatic carcinoma prostate | 0 |
| A.D. | 55 | Metastatic carcinoma to brain, bronchiogenic | 0 |
| L.R. | 50 | Metastatic carcinoma to brain, bronchiogenic | 0 |
| R.A. | 5 | Encephalopathy ? etiology | 0 |
| J.F. | 65 | Metastatic carcinoma, bronchiogenic | 0 |
| T.M. | 62 | Metastatic carcinoma, esophageal | 0 |
| R.H. | 2 | Encephalopathy ? etiology | 0 |
| A.G. | 47 | Metastatic carcinoma to brain, bronchiogenic | 0 |
| C.M | 11 | Cerebral and cerebellar degeneration, ? cause | 0 |
| J.C. | 2 | Encephalopathy, ? cause | 0 |
| W.T. | 1 | Encephalopathy, ? cause | 0 |
| C.B. | 11 | Diabetes mellitus | 0 |
| S.U. | 1 | Convulsive disorder ? cause | 0 |
| J.F. | 3 | Chronic meningoencephalitis ? cause | 0 |
| D.W. | 2½ | Subdural hematoma, 2 weeks postoperatively | 0 |
| J.P. | 5 | Mongolian idiocy | 0 |
| B.B. | 10 | Meningomyelocele | 0 |
| M.P. | 78 | Senile dementia | 0 |
| S.B. | 7 | Rheumatoid arthritis | 0 |
| | | R. spastic hemiplegia since birth | 0 |
| M.H. | 2½ | Convulsive disorder | 0 |
| J.M. | 12 | Rheumatic fever | 0 |
| C.S. | 5 | Cerebellar neoplasm | 0 |

material) blue. Three per cent neutral red and 4 per cent safranin also stain the structures no differently from other sediment material. A modification of the periodic acid spot test[14] gave no differential staining, although structures consistent with granular bodies were stained a distinct pink with this technic.

Like the material in kidney and brain, that in the urine does not stain for neutral fats with Sudan IV by a method reliably applied to the urine sediment.[15] An adaptation of the Turnbull blue method for ferrous iron and the Schmorl method was not revealing.[16] The benzidine test was negative.[17]

*Control Studies*

Whether a given sample of sediment is positive or negative is ultimately a visual interpretation. An extensive background of experience in the artifacts in normal and abnormal urine is essential to avoid false positive or negative interpretations.

A selected control series of 110 pertinent cases has been negative for the characteristic findings of metachromatic leukoencephalopathy (tables 1 and 2).* Included among the negatives are:

1. Fourteen unaffected siblings and unaffected parents in three different families. This is the ultimate control group. These establish that the urine sediment findings are confined to the affected members of a family.

2. Twenty-two cases of acute and chronic demyelinating disease of various kinds. This includes massive cerebral infarctions, multiple sclerosis, and peripheral nerve demyelination. These indicate that other forms of demyelination of various ages and amounts do not cause these findings.

3. Twenty cases of heredodegenerative disease, including six with clinically tenable diagnosis of diffuse sclerosis, one pathologically proved. They indicate that these genetically determined demyelinations or degenerations *per se* do not cause these findings, nor do other forms of diffuse sclerosis.

4. Twelve cases of renal, eight cases of hepatic, five cases of muscular, and 29 cases of miscellaneous diseases. These establish that the presence of disease in a variety of organs (some of which may be involved in this disorder, too) is not responsible for the observed urine changes.

Some patients with metachromatic leukoencephalopathy may have carotenemia which reflects their lowered metabolic rate, special strained food intake, and possibly other factors.[1] Because the orange color of their plasma was similar to the delayed golden-brown color of the stained (but not the unstained) granule bodies, this point was studied further. Two other cases of human carotenemia (one with myxedema) had no urine abnormalities, nor did a third person on a high carotene intake. One 170 gm. white rat (Sherman strain) was exposed to massive oral dosages of beta-carotene for three weeks (5 mg. beta-carotene in 0.1 cc. linseed oil per day). No pertinent changes occurred in kidney sections or in urine. These observations indicate that a coincidental carotenemia is not responsible for the urinary findings.

Urine sediment from five dogs had no characteristic abnormalities, although in contrast to man, some lipid is reported

*Most of the patients in this control series were studied on the various university services of the Columbia-Presbyterian Medical Center, New York City, and at the Doernbecker Memorial and Multnomah County Hospitals of the University of Oregon Medical School, Portland, Oregon.

normally in dog and cat kidney tubules.[18,19] Frozen sections of dog and cat kidneys stained with toluidine blue showed none of the metachromatic findings observed in humans. These observations indicate that the renal lipid in these animals is not itself sufficient to cause these urinary findings.

*Pitfalls*

These include inexperience, old urine specimens, heavy urine urate content, pyuria, artifacts, inadequate searching, contamination of a negative sediment by true metachromatic structures not washed out of the bottom of a previously used centrifuge tube, and so on. With experience, the structures described are characteristic and, thus far, specific. Until this is gained, it would appear preferable to have diagnosis during life confirmed by frozen sections of kidney obtained by biopsy (figure 1). It is quite probable that the overt childhood forms of metachromic leukoencephalopathy will simultaneously have a metachromatic nephropathy, permitting diagnosis from the urine sediment. It is clear that the uncommon case which has no renal tubular deposits will not be detected by this method.[20]

*Other Urine Studies*

The urines are not otherwise distinctive for color, odor, specific gravity, pH, glucose, acetone, albumin, or sediment content. The further biochemical identification of the metachromatic materials is in process.

## SUMMARY AND CONCLUSIONS

1. Since 1953 five cases of the metachromatic form of diffuse sclerosis have been diagnosed for the first time during life by a technic of urine examination.

2. Pertinent features of this disorder and of the case material of this report are briefly reviewed.

3. The diagnostic procedure is based on two principal observations: first, that abnormal material may be found in the centrifuged urine sediment, and second, that it may there be distinctively stained with certain aniline dyes.

4. The granular material in urine sediment originates from that in the convoluted, looped, and collecting tubules of the kidney. It takes six descriptive forms. Each becomes a golden-brown metachromatic color with toluidine blue, is soluble in certain organic solvents, and is doubly refractile like that in the kidney tubules.

5. Preliminary observations of the staining properties and migration characteristics of the material are consistent with its having a negatively charged component.

6. The urine sediment findings have been found to run parallel to the clinical course of the disease.

7. The reliability of the method in practice is substantiated by autopsies, by renal biopsy, by a selected control series of 110 human cases, and by animal controls.

8. The laboratory diagnosis and measurement of the course of this diffuse demyelinating disease is therefore possible.

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■ The predisposition to epilepsy, in whatever it consists, is evidently increased by a plethoric state of body. Almost all writers have placed plethora among the predisposing causes of this malady. Hippocrates remarks that epilepsy prevails in the spring; and that a fulness of habit is one of its most frequent causes. A celebrated writer thinks that this state of body may so affect the soundest brain as to produce the epileptic disposition, which, when once formed, may be renewed on slight occasions. – That plethora is very frequently connected with this complaint no person can doubt. In almost every case which I have had an opportunity of seeing, the disease has occurred in full habits and sanguine temperaments. An ingenious writer, however, is of opinion that there is no temperament which is in a very decided manner more subject to epilepsy than others. He has witnessed its appearance in every variety of habit, from the most exquisite examples of the sanguine to the most marked melancholic.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

# Functional Relationships Between the Red Nucleus and the Brachium Conjunctivum

## Physiologic Study of Lesions of the Red Nucleus in Monkeys with Degenerated Superior Cerebellar Brachia

*Malcolm B. Carpenter, M.D.**

THE SYNDROME OF BENEDIKT,[1–3] as described in the clinicopathologic literature, consists of homolateral, complete or incomplete, oculomotor palsy, contralateral abnormal involuntary activity (usually ataxia, tremor, and asynergic phenomena), and often some degree of paresis. Vascular lesions of the mesencephalic tegmentum localized to the red nucleus, third nerve fibers, and sometimes part of the cerebral peduncle have been reported most commonly in this syndrome. This syndrome would suggest that well localized lesions in the red nucleus in the monkey might produce deficits of a similar character. Numerous investigators have produced such lesions in various experimental animals[4–11] and none have resulted in physiologic disturbances equivalent to those found in man.

In the rhesus monkey stereotaxic lesions of the red nucleus[11] produced 1) enduring hypokinesis which did not impair the quality of motor performance, and 2) transient ataxia, tremor (usually combined simple and ataxic), and asynergic phenomena. Unilateral or asymmetric lesions of the red nucleus in some animals provoked tilting and rotation of the head to the opposite side, but there is some question as to whether this is specific for the red nucleus. It did not seem that this unexpected result could be accounted for by phylogenetic differences alone. Even if lesions of the red nucleus itself do not provoke motor disturbances other than hypokinesis, this does not explain the absence of disturbances which would be expected from concomitant destruction of the main ascending limb of the brachium conjunctivum as it traverses the red nucleus in its course to the diencephalon. Previous investigations indicate that interruption of the brachium conjunctivum at the level of the red nucleus or above in the monkey does not produce the enduring physiologic deficits (ataxia, ataxic tremor, tremor, and asynergic phenomena) that result from removal of the deep cerebellar nuclei or section of the su-

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perior cerebellar peduncle caudal to the red nucleus.

The present study was directed at determining the physiologic effects of localized lesions in the red nucleus in monkeys with degenerated brachia conjunctiva. It was felt that, if the brachium conjunctivum could be eliminated by degeneration, study of the effects of tissue deficits in the red nucleus might be facilitated. By these means it was hoped to arrive at a better understanding of the functional relationship between the red nucleus and the brachium conjunctivum.

## MATERIAL AND METHODS

Eleven rhesus monkeys of both sexes with weights ranging from 2,500 to 4,000 gm. were used. In ten monkeys attempts were made to destroy significant portions of the deep cerebellar nuclei (that is, fastigial, interposed, and dentate nuclei) bilaterally by inserting a small glass suction tube into the interior of the cerebellum. In one additional animal the right brachium conjunctivum was sectioned caudal to the inferior colliculus with a small knife. The methods used have been described elsewhere.[12] Animals were observed for approximately 200 days following the primary surgical procedure, during which time detailed observations were made at regular intervals and neurologic examinations were made periodically. Cinematographic records were taken of all animals exhibiting noteworthy physiologic deficits.

After the 200-day observation period, attempts were made to produce localized lesions in the red nuclei of these 11 animals by stereotaxic methods.[11,13] Detail observations, neurologic examinations, and cinematographic records were made following the second surgical procedure. After a survival period of at least 14 days beyond the second surgical procedure, animals were examined neurologically, anesthetized with intravenous Nembutal, and sacrificed by intracardiac perfusion with 600 ml. of 10 per cent neutral formalin. The brains of these animals, after further fixation in formalin, were sectioned perpendicular to the axis of the brainstem, impregnated according to the Marchi method, and embedded in celloidin. Serial sections were cut at 23 microns and every tenth section was mounted.

*Analysis of the lesions.* Lesions of the deep cerebellar nuclei were mapped on outline drawings to reveal the spatial disposition of destruction of the cerebellar nuclei. Outline drawings were made of the portions of the brachium conjunctivum containing dense Marchi degeneration (figure 1).

Outline drawings of the red nuclei and the portions of the nuclei destroyed were obtained by projecting serial sections in an Edinger apparatus at a magnification of 20. Areas of the projected outline were measured in square millimeters with a Keuffel and Esser polar planimeter. From these data planimetric profiles of the red nuclei and the lesions within the nuclei were constructed, using square millimeters as the ordinate and sectional planes (23 microns) as the abscissa. Using these planimetric profiles, estimations of the volume of the red nucleus and the portions of the nucleus destroyed were made.[11,14]

## OBSERVATIONS

The physiologic disturbances and anatomic degenerations resulting from complete and partial lesions of the deep cerebellar nuclei and brachium conjunctivum in the monkey have been reported in detail.[12] In brief, lesions of the deep

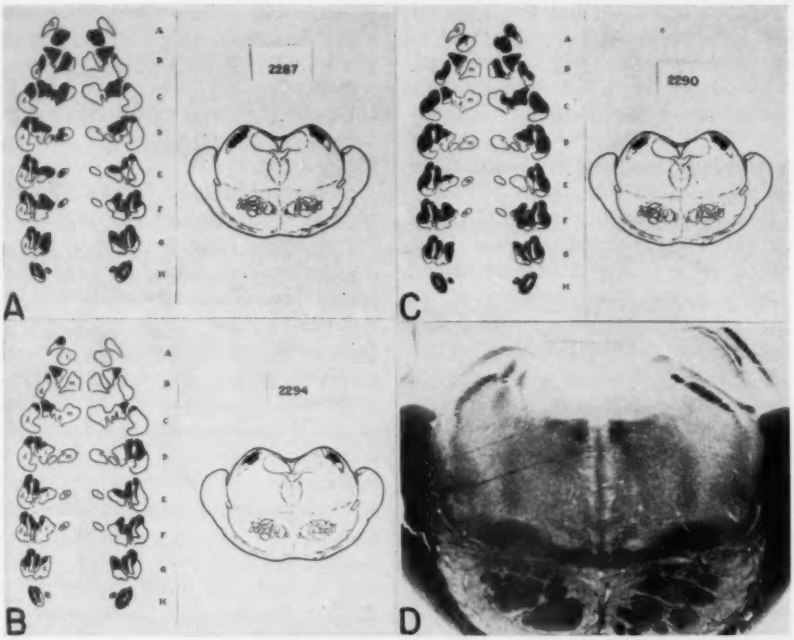


FIG. 1. The outline drawings *A*, *B*, and *C* represent serial drawings of the deep cerebellar nuclei and a transverse section of the upper pons. The black areas indicate the spatial disposition of destruction within the deep cerebellar nuclei and, in the case of the brachium conjunctivum, the location of Marchi degeneration. *D* is a photomicrograph of a section through the upper pons in rhesus 2282, showing marked attenuation of both superior cerebellar brachia due to lesions of the deep cerebellar nuclei and small direct lesions of both brachia conjunctiva. Marchi stain.

cerebellar nuclei produce severe ataxia, ataxic tremor, asynergic phenomena, simple tremor (tremor at rest), mild alterations of muscle tone (hypotonus), hypokinesis, and sometimes disturbances of equilibrium. Of these physiologic deficits, ataxia, hypokinesis, and hypotonus appeared to persist with the least attenuation during the 200-day observation period. Ataxic tremor was always associated with ataxia, but tended to disappear while generalized ataxia was still detectable. This type of tremor was considered an asynergic manifestation related to ataxia, and probably dependent upon it, which involved particularly the proximal muscle groups of the shoulder and arm; activity present in the more peripheral portions of the extremity seemed to be mechanically transmitted from the proximal appendicular musculature. Simple tremor occurred only in association with ataxia and ataxic tremor; it never was observed as an isolated type of dyskinesia. This type of tremor always disappeared prior to ataxic tremor and usually was present for less than four weeks. In none of these animals was simple tremor seen longer than 100 days.

Attempts to produce secondary stereotaxic lesions in the red nuclei were suc-

cessful in four (2282, 2287, 2290, and 2294) of the ten animals with bilateral lesions of the deep cerebellar nuclei and in the one animal (2210) with unilateral destruction of the brachium conjunctivum. The physiologic effects of the red nucleus lesions in these five animals form the substance of this report.

*Primary lesions.* In three (2287, 2290, and 2294) of the four animals with lesions of the deep cerebellar nuclei, primary lesions were confined to the deep cerebellar nuclei and the medullary core of the cerebellum; the brachium conjunctivum was not directly damaged either within or outside of the cerebellum. Outline drawings of the spatial disposition of the destruction within the deep cerebellar nuclei and the resulting Marchi degeneration within the superior cerebellar peduncle are presented in figure 1. In rhesus 2282 the primary lesions destroyed portions of the deep cerebellar nuclei bilaterally, but concomitant direct injury to both superior cerebellar brachia was present also. The greatly attenuated brachia and the location of the direct lesions are shown in figure 1. The entire right brachium conjunctivum was sectioned caudal to the inferior colliculus in rhesus 2210 (figure 3).

*Primary physiologic deficits.* Duration of the most prominent physiologic deficits resulting from the primary lesions is tabulated in table 1. Generalized ataxia, probably the most marked disturbance, became somewhat attenuated during the approximately 200-day observation period, but was still readily detectable in all animals at the time of the secondary surgery. Ataxia and asynergic disturbances seemed greatest in the upper extremities. These animals were hypokinetic, and climbing and walking were always performed awkwardly. Ataxic tremor was present as long as ataxia in three animals (2210, 2282, and 2294) and in the other two animals it disappeared after 131 (2287)

TABLE 1

SUMMARY OF PHYSIOLOGIC FINDINGS IN 5 MONKEYS

| *Animal No.* | 2210 | 2282 | 2287 | 2290 | 2294 |
|---|---|---|---|---|---|
| Total survival (days) | 221 | 230 | 210 | 229 | 212 |
| | | PRIMARY SURGERY | | | |
| Survival after primary surgery† (days) | 201 | 216 | 184 | 210 | 198 |
| Duration (days): | | | | | |
| A. Ataxia | 201 | 216 | 184 | 210 | 198 |
| B. Ataxic tremor | 201 | 216 | 131 | 186 | 198 |
| C. Head tremor | 181 | 89 | 56 | 205 | 42 |
| D. Simple tremor | 100 | 89 | — | 18 | 100 |
| | | SECONDARY SURGERY | | | |
| Survival after secondary surgery‡ (days) | 20 | 14 | 26 | 19 | 14 |
| Duration (days): | | | | | |
| A. Ataxia | 20 | 14 | 26 | 19 | 14 |
| B. Ataxic tremor | 17 | 14 | 1 | 19* | 14* |
| C. Head tremor | 2 | + | — | — | — |
| D. Simple tremor | — | — | — | + | 14 |
| Degree of hypokinesis | Increased | Increased | Increased | Increased | Unchanged |
| Choreoid activity | ++ | | ++ | | |

† Lesions of the deep cerebellar nuclei or brachium conjunctivum
‡ Lesions of the red nuclei (see table 2)
* Activity increased in severity
+ Intermittent
++Observed only once

and 186 (2290) days. Ataxic tremor, like ataxia, was most prominent in the upper extremities; it seemed to show a greater attenuation with time, becoming less coarse and of smaller amplitude. Simple tremor, observed in four of these five animals, occurred mostly in the upper extremities, had a flexion-extension pattern involving the muscles of the arm, forearm, and hand, and in all animals disappeared while ataxic tremor was still present. In two of the animals simple tremor persisted for 100 days. Head tremor, listed as a separate category because it seemed to be a combination of both simple and ataxic tremor, was of variable duration. In general it was greatest immediately after surgery and subsided with time. All of these animals were hypokinetic immediately after surgery and tended to remain so even after the severity of the cerebellar disturbances had subsided greatly.

*Lesions of the red nuclei.* Lesions of the red nuclei were produced bilaterally in four animals and unilaterally in one (2294). In table 2 data are presented concerning the volume of red nuclei, the volume of red nuclei destroyed by the lesions, and percentile estimates of the volume of the red nuclei destroyed in the rostral and caudal halves of the nuclei (figures 2 and 3).

*Red nucleus lesions in animals with partial degeneration of the brachium conjunctivum.* Three (2282, 2287, and 2290) of these four animals exhibited markedly increased hypokinesis following stereotaxic lesions of the red nuclei. Hypokinesis was manifest by extreme reluctance to move about in the usual simian fashion and was greater than that present after the primary lesions of the deep cerebellar nuclei. In one of these animals (2282) the degree of hypokinesis was so severe as to resemble that seen in association with bilateral lesions of the globus pallidus. In the fourth animal (2294) no significant change was noted in the kinetic state.

The generalized ataxia present prior to placement of lesions in the red nuclei persisted without remarkable change. Some increase in the severity of ataxia

TABLE 2
SECONDARY LESIONS OF THE RED NUCLEI

| Animal No. | | Volume of the Red Nucleus ($mm^3$) | Volume of the Red Nucleus Destroyed ($mm^3$) | Volume of the Red Nucleus Destroyed Per Cent | Percentile Volumes of the Red Nucleus Destroyed* Rostral Half Nucleus | Percentile Volumes of the Red Nucleus Destroyed* Caudal Half Nucleus |
|---|---|---|---|---|---|---|
| 2210 | Right | 9.5 | 1.5 | 15.5 | 20 | 6.4 |
| | Left | 13.1 | 5.0 | 38.1 | 55.8 | 12.9 |
| 2282 | Right | 9.9 | 0.2 | 2.0 | 3.0 | 0 |
| | Left | 10.6 | 2.7 | 25.0 | 32.9 | 6.5 |
| 2287 | Right | 7.8 | 0.4 | 5.1 | 0 | 12.4 |
| | Left | 8.4 | 0.4 | 4.7 | 0 | 12.1 |
| 2290 | Right | 10.1 | 5.0 | 49.5 | 42.6 | 39.8 |
| | Left | 9.1 | 2.8 | 30.5 | 39.1 | 21.8 |
| 2294 | Right | 11.9 | 5.2 | 43.7 | 56.7 | 24.5 |
| | Left | 10.9 | – | – | – | – |

*The volumes of the rostral and caudal halves of the red nucleus were determined by dividing in half the total number of serial sections in which the red nucleus appeared and calculating the respective volumes by using planimetric profiles. Although the same number of serial sections were present in the rostral and caudal halves of the nucleus, the volume of the rostral half was larger because the caudal part of the nucleus is tapered. The ratio of the volumes of the rostral half of the nucleus to the caudal half, when divided on this linear basis, is approximately 1.8 to 1.

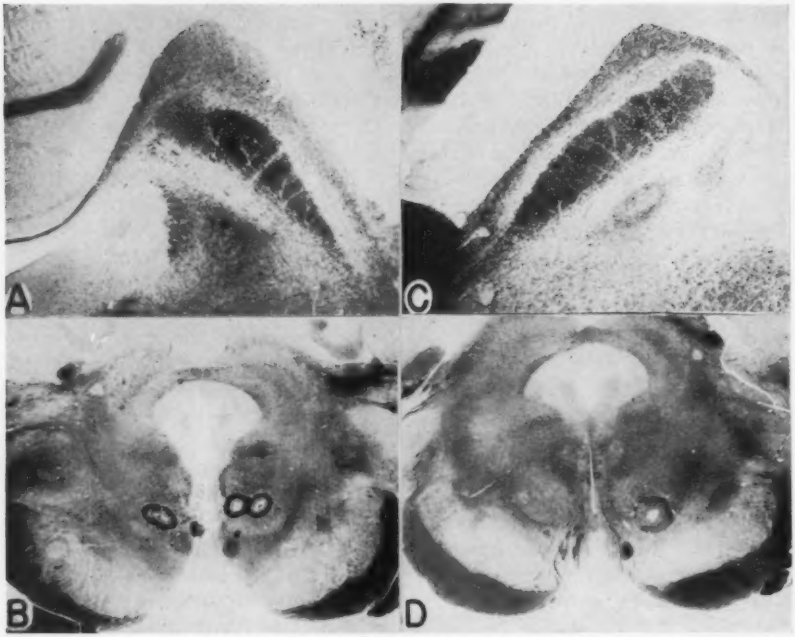


FIG. 2. Photomicrograph *A* shows the location of Marchi degeneration in the right brachium conjunctivum in rhesus 2290, and *B* shows the location of stereotaxic lesions within the red nuclei in the same animal. Photomicrograph *C* shows the location of Marchi degeneration in the left brachium conjunctivum in rhesus 2294, and *D* shows the stereotaxic lesion in the right red nucleus in the same animal. Marchi stain.

was evident immediately after surgery, but subsided about the third postoperative day, except in rhesus 2290 and 2294.

Following lesions of the red nuclei, ataxic tremor was increased in one animal (2294), reappeared in two others (2287 and 2290) that had not exhibited it prior to secondary surgery, and was unchanged in rhesus 2282. In rhesus 2294 ataxic tremor was present in both upper extremities prior to secondary surgery, but was of small amplitude and appeared only sporadically, particularly prior to and at the termination of movement (propraxic and epipraxic tremor). Following a lesion of the right red nucleus, ataxic tremor became more frequent in occurrence and its amplitude was increased. Tremor consisted of a flexion extension pattern at the elbow, wrist, and digits. Associated with the increased ataxic tremor was the re-appearance of simple tremor (tremor at rest) in both upper extremities, consisting of alternate supination and pronation of the forearms combined with small amplitude flexion and extension of the hands at the wrist. Activity appeared maximal in the forearms and seemed to be mechanically transmitted to the distal portions of the extremities. Both ataxic and simple tremor persisted without attenuation until sacrifice.

Ataxic tremor re-appearing in rhesus 2290 following lesions in the red nuclei was of moderate amplitude and coarse-

ness and resembled the type of tremor observed after the primary lesions of the deep cerebellar nuclei. Ataxic tremor in this animal persisted until sacrifice 19 days later. The ataxic tremor re-appearing in rhesus 2287 after secondary lesions was seen only on the first postoperative day.

Following red nucleus lesions, simple tremor appeared in only two animals (2290 and 2294) in association with ataxic tremor. It was most pronounced and continuous in rhesus 2294, as described above. In the other animal (2290) simple tremor in both upper extremities occurred only intermittently but was unequivocal.

Choreoid activity was seen in the left lower extremity in rhesus 2287 on the first postoperative day. It was almost identical to that seen in rhesus 2210 in that it involved particularly the peripheral portions of the extremity. The foot was rotated at the ankle and the digits were flexed and extended repeatedly. The choreoid activity resembled that seen following lesions of the subthalamic nuclei, except that more distal appendicular musculature was involved and the activity was never violent. No activity even suggesting choreiform movement was seen in any of the other animals.

Aside from occasional falling to one side or a tendency to fall in the immediate postoperative period, none of these animals exhibited disturbances of equilibrium except rhesus 2287. Following primary surgery this animal was seen to climb up one side of the cage and reverse its position so that the head was directed downward. In this position the head was rotated in a circular fashion. While sitting upright the head was frequently thrown backward and rotated in a counterclockwise direction. This curious rotation of the head persisted for about two weeks and then disappeared. After placement of rather small lesions in the red nuclei, reappearance of the rotating circular movements of the head was seen, but only for one day.

Muscle tonus was usually reduced in these animals after lesions of the deep cerebellar nuclei, although no apparent change in tonus was noted in some animals. Following secondary lesions of the red nuclei, muscle tonus, as estimated by resistance to passive movement, was reduced in all animals.

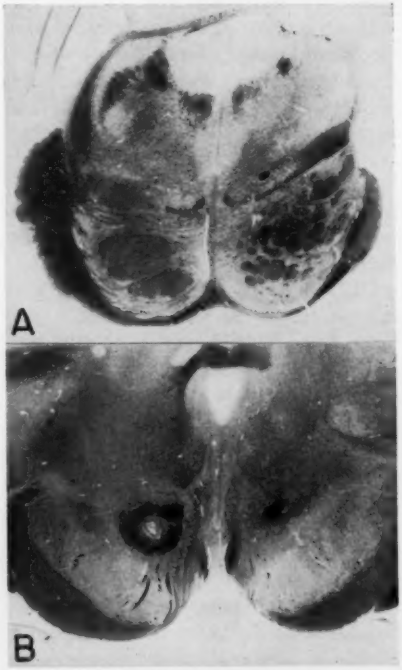


FIG. 3. Rhesus 2210. In photomicrograph *A* the right brachium conjunctivum is totally degenerated as a consequence of surgical section of this structure caudal to the inferior colliculus. In photomicrograph *B* the lesions of the red nuclei can be seen. Marchi stain.

The deep tendon reflexes following lesions of the red nuclei exhibited an increased threshold, reduced force, and a somewhat pendular quality.

*Red nucleus lesions in the presence of total degeneration of the brachium conjunctivum.* In rhesus 2210 the right brachium conjunctivum was sectioned completely caudal to the inferior colliculus. Marked ataxia, dysmetria, asynergic phenomena, ataxic tremor, and simple tremor were observed in the right extremities following surgery for the intervals noted in table 1. Two hundred and one days after the primary surgery ataxic tremor and asynergic disturbances were still evident in the right extremities, though in an attenuated form, and occasional head tremor was seen. Neurologic examination revealed 1) a probable left homonymous hemianopsia (right occipital lobe was amputated), 2) probable impairment of appreciation of pain and pressure sensations in the left upper extremity, and 3) absent grasp reflexes in all extremities.

Following placement of bilateral stereotaxic lesions in the red nuclei (see table 2 for location and percentile volumes of the nuclei destroyed), the animal was unable to stand or walk for a few days, but managed to maintain an upright sitting posture with all limbs abducted and partially extended. Occasional falling from this sitting position was seen, usually to the right side. Initially, considerable ataxia and asynergia were present in all extremities, but after the eighth postoperative day they were seen only on the right side. No paresis could be detected and muscle tone seemed to be within normal limits. The animal was profoundly hypokinetic by comparison with previous activity. On the third postoperative day slow choreoid activity of an unequivocal character was observed for a period of at least an hour in the left lower extremity. This activity was neither violent nor forceful and appeared to involve only the distal portions of the extremity. No choreoid activity was ever seen after this day.

After the eighth postoperative day the animal appeared essentially the same as prior to placement of the lesions in the red nuclei, except that the degree of hypokinesis was much greater. Ataxia and ataxic tremor persisted in the right extremities without change until sacrifice.

## DISCUSSION

Lesions of the deep cerebellar nuclei and direct lesions of the brachium conjunctivum below the decussation in the monkey[12] almost invariably produce ipsilateral ataxia, asynergia, and ataxic tremor which, though enduring, undergo some attenuation with time. Simple tremor is sometimes seen also, but is not as prominent as the other disturbances. Isolated lesions of the red nucleus in the monkey[11] which do not directly involve fibers of the brachium conjunctivum below the red nucleus rarely produce any lasting dyskinesia. Since the latter lesions by their very nature destroy a considerable proportion of the main ascending fibers of the brachium conjunctivum, the question arises whether preservation of the red nucleus or parts of it is essential to maintenance of dyskinetic disturbances resulting from interference with cerebellofugal fiber systems. There is still no evidence that lesions of the brachium conjunctivum above the red nucleus produce dyskinesia. The present investigation may offer a partial explanation of these phenomena.

In one animal (2210) the entire right

brachium conjunctivum was sectioned surgically and degeneration of the entire bundle of fibers was confirmed histologically. Subsequent lesions of the red nuclei destroying a significant portion of the nuclei did not alter the dyskinesia on the right side. In animals 2282 and 2287 with extensive but incomplete degeneration of both superior cerebellar peduncles, red nucleus lesions did not provoke significant changes in the ataxia or ataxic tremor. In rhesus 2294, with the least amount of degeneration in the brachia conjunctiva, a recrudescence of ataxia and ataxic tremor was seen following lesions of the red nuclei. Simple tremor returned following secondary lesions in both 2290 and 2294, but was only intermittent in the former animal. It might be presumed that reappearance of ataxic and simple tremor in these animals resulted from destruction of fibers of the brachium conjunctivum previously undegenerated. In those animals in which the secondary lesions of the red nuclei resulted in reappearance of ataxic and simple tremor, degeneration in the brachium conjunctivum was not only less complete but different in location. In rhesus 2290 and 2294 a greater proportion of fibers located in the dorsomedial part of the brachium conjunctivum were preserved than in rhesus 2282 and 2287. In all animals with incomplete degeneration of the brachia conjunctiva, fibers located ventrolaterally were preserved at least in part. Fibers originating from the interposed and the dorsal part of the dentate nuclei were found to occupy the dorsomedial part of the brachium conjunctivum.[12] Lesions of the deep cerebellar nuclei provoking degeneration in this part of the brachium were associated with particularly severe ataxia. Thus the ataxic and simple tremor seen in rhesus 2290 and 2294 may have resulted from an increase in the degree of ataxia; ataxic and simple tremor appear to bear a definite direct relationship to ataxia. Fibers occupying the ventrolateral portion of the brachium conjunctivum originate largely, if not exclusively, in the ventral part of the dentate nucleus and project to the globus pallidus as well as the lateroventral nucleus of the thalamus. The ventrolateral portion of the brachium conjunctivum is the only part of this structure containing fibers projecting to the pallidum.[12,15]

Although choreoid activity has been reported to occur in man in association with localized lesions of the red nucleus, this type of dyskinesia has not been produced in the monkey by such lesions.[11] In the author's experience, neither complete nor partial lesions of the brachium conjunctivum nor lesions of the deep cerebellar nuclei have produced choreoid activity. Isolated lesions of the ventral part of the dentate nuclei have not been produced and this may be significant. Carrea and Mettler[16] reported transient choreiform activity in three monkeys (206 T, 1162, and 2009) as a consequence of bilateral lesions of the brachium conjunctivum, thus at least indicating that this may be the crucial structure. Except for the investigations cited, the only lesions known to consistently provoke choreoid activity in experimental animals are those localized to the subthalamic nucleus of Luys.[17–19]

Choreoid activity seen following secondary lesions of the red nuclei in two animals of the current series resembled that seen in association with lesions of the subthalamic nucleus, except that the activity involved particularly the distal portions of the lower extremity and the activity was not violent. The lesion re-

sponsible for choreoid activity in rhesus 2210 was located in the right red nucleus. Since the brachium conjunctivum was totally degenerated on the right side and no choreoid activity occurred on the right side as a consequence of the primary lesion or the secondary lesion in the left red nucleus, it was concluded that lesions of the red nucleus itself could not be responsible for the observed choreoid activity. Choreoid activity seen on the left in this animal must have resulted from interruption of fibers of the brachium conjunctivum within the right red nucleus. Rhesus 2287 in which choreoid activity appeared also on the left side is significant because it yields information concerning the location of fibers within the brachium conjunctivum which may be concerned with choreiform activity. In this animal choreoid activity on the left side resulted from a lesion in the right red nucleus. However, since lesions of the red nucleus do not produce choreoid activity, the choreoid activity must have resulted from interruption of the only fibers of the brachium conjunctivum which were not degenerated, namely those located in the ventrolateral region. Thus these cases seem to indicate that interruption of the fibers from the ventrolateral part of the brachium conjunctivum at the level of the red nucleus may produce choreoid activity contralaterally. It is significant that these fibers located in the ventrolateral part of the brachium conjunctivum are the only ones which in part project to the globus pallidus via the dorsal and ventral divisions of the ansa lenticularis.

The relationship between lesions of the red nuclei and hypokinesis seems of particular importance. Monkeys with discrete lesions of the red nuclei are extremely hypokinetic but do not show impairment of general motor performance. Although these animals show extreme reluctance to move about, they behave in perfectly normal fashion when threatened or excited and defend themselves with great ferocity. The similarity between these animals and those with bilateral pallidal lesions was at once apparent. Originally it was felt that the hypokinesis seen following lesions of the red nuclei was a consequence of interruption of fibers projecting from the red nuclei to the pallidum, but subsequent studies[20] have shown that hypokinesis also results from interruption of the rubrospinal tract. It would thus appear that the red nucleus and its spinal projections are concerned with maintenance of kinetic activity and that deficits resulting from damage to this system depress voluntary and associated activity. It is of interest that the hypokinesis associated with lesions of the deep cerebellar nuclei and the efferent fiber systems originating from them can be further increased as a result of lesions of the red nuclei. This suggests that the systems may function synergistically to regulate the kinetic state and that the red nucleus and its descending projections is the more potent element in the rhesus monkey.

## SUMMARY AND CONCLUSIONS

An attempt was made to determine the physiologic effects of localized lesions in the red nucleus in monkeys with complete and partial degeneration of the superior cerebellar peduncles. In ten rhesus monkeys portions of the deep cerebellar nuclei were removed by suction, and in one additional animal the brachium conjunctivum was completely sectioned caudal to the inferior collicu-

lus. After observing these animals for periods of approximately 200 days, attempts were made to produce secondary stereotaxic lesions in the red nuclei. The latter procedures were successful in five animals. Serial sections of the brains and portions of the spinal cords were prepared by the Marchi method.

The following conclusions were drawn:

1. Lesions of the red nuclei in the monkey produce marked hypokinesis and increase the degree of hypokinesis associated with lesions of the deep cerebellar nuclei and the brachium conjunctivum.

2. In monkeys with complete or virtually complete degeneration of the brachium conjunctivum, lesions of the red nuclei do not significantly alter ataxia, ataxic tremor, or asynergic disturbances.

3. Lesions of the red nuclei may provoke an increase in ataxia and a reappearance of ataxic and simple tremor in monkeys with partial degeneration of the brachium conjunctivum, particularly if fibers in the dorsomedial portion of this structure have been preserved.

4. Transient choreiform activity may result from localized lesions of the red nucleus, but only if portions of the brachium conjunctivum are undegenerated.

The hypothesis is presented that dyskinetic phenomena resulting from localized lesions of the red nucleus in the monkey are a consequence of interruption of ascending fibers of the brachium conjunctivum rather than destruction of the cells in the red nucleus.

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# A Rare Electroencephalographic Pattern: The Six per Second Spike and Wave Discharge

*Juergen Thomas, M.D.**

IN THE PROCESS of recording routine electroencephalograms, a distinct but rather rare seizure pattern has been identified. We have called this abnormality six per second spike and wave discharge.[1] The present report deals with the form of this discharge, its voltage distribution over the head, age distribution, and clinical correlations.

## CASE MATERIAL

The 210 cases selected for this study were sorted from a total material of approximately 30,000 electroencephalograms, which included normal control subjects and patients with epilepsy, brain tumor, and a wide variety of neurologic and psychiatric disorders. Out of these recordings about 20,000 showed some type of seizure discharge, but only 1 per cent had six per second spike and wave discharges in pure culture, that is, as the only abnormality.

The six per second spike and wave, like all other patterns that are associated with epileptic symptoms, can be found occasionally in persons who consider themselves entirely well and asymptomatic. The percentage incidence of this pattern in normal control subjects has not been accurately determined.

## METHOD

Electroencephalograms were recorded with an eight-channel Grass electroencephalograph, using the monopolar method with ear leads as references. All recordings were made in both the waking and sleeping states.

## RESULTS

The age distribution curve (figure 1) shows that six per second spike and wave discharges occur most commonly among adolescents and young adults. They are found occasionally in young children and older adults. There is a slight preponderance of females over males; 58 per cent of the present series were women and 42 per cent were men.

The six per second spike and wave pattern has its most consistent and characteristic form in adults. Beyond the age of 30 years it usually appears as a synchronous and bilaterally symmetric discharge in the parietal and occipital areas without a focal onset. A typical example is shown in figure 2a. The pattern can be described as follows: A low voltage spike with a duration of approximately 1/30 of a second is followed by a slow rounded wave with a duration of approximately 1/6 second. The spike is sharp and diphasic; a strong negative

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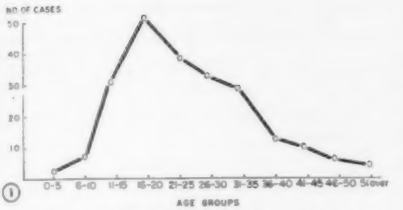


FIG. 1. Age distribution of patients with six per second spike and wave discharges.

phase usually precedes the positive phase, but sometimes it is triphasic with an initial positive deflection. The slow wave immediately following the positive spike has a dome-shaped appearance. The pattern would repeat six times in one second, but the burst is usually very short and as a rule includes only three or four spike-and-wave components.

The six per second spike and wave formation could be called "miniature petit mal" because it bears a pictorial resemblance to the three per second spike and wave of petit mal, but so many features and correlates of this disorder are different from petit mal (as will be shown in a later part of this report) that it would seem best not to use this term. What is referred to here as the six per second spike and wave discharge may be related to Walter's "phantom petit mal",[3] at least this is suggested by Marshall.[2]

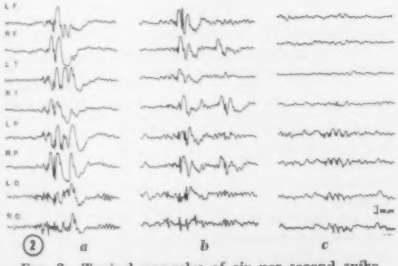


FIG. 2. Typical examples of six per second spike and wave patterns of a child, an adolescent, and an adult, shown in that order from left to right.

Among adults the highest voltage of the discharge is usually in the parietal and occipital areas. However, when all age groups are considered, variations with age are apparent in the six per second spike and wave pattern. In general, the younger the individual the slower the frequency, the higher the amplitude, and the more generalized the discharge. In the five to 15 year age range, the frequency is often as low as four per second and the amplitude is often three to four times higher than in adults. Among children the discharge is not only more generalized than among adults as a rule, but it commonly has a high voltage in the frontal areas (figure 2a). This contrasts with the situation among 30 to 50 year old adults, where the highest voltage is usually in the parietal and occipital areas.

The six per second spike and wave discharge was found in all cases during drowsiness, but in 25 per cent of the total series in which it was present it appeared also in the waking state and in only 7 per cent was it present during the spindle phase of sleep (figure 3). Waking background activity was normal or with very few exceptions borderline normal. Other patterns of drowsiness and sleep were normal.

Analysis of the patients' symptomatology showed that 124 cases or 59 per cent of the total group suffered from convulsive seizures. In addition, roughly one-half had histories of other paroxysmal symptoms. The types of convulsive seizure are listed in table 1. The most striking finding in this group was the high incidence of grand mal, the low incidence of psychomotor, and the complete absence of petit mal epilepsy.

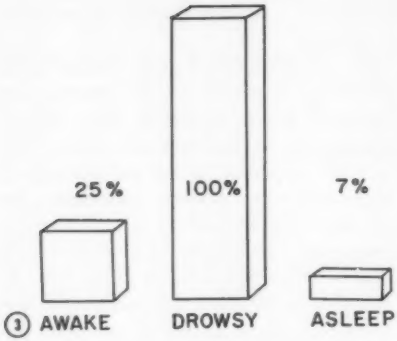


FIG. 3. Percentage of cases in which six per second spike and wave discharges appeared in the waking, drowsy, and sleeping states (percentages are nonexclusive).

Nonconvulsive paroxysmal symptoms were the only findings in 43 cases (the types of episode are listed in table 2). When these cases are included, the number of patients with ictal symptomatology is 167, or almost 80 per cent of the total group with six per second spike and wave discharges. The remaining 43 patients (or 20 per cent of the total) were not reported as having any paroxysmal symptoms. The nature of their symptomatology is indicated in table 3.

REPEAT STUDIES

Repeat electroencephalograms were made on 41 patients, all of them belonging to the epileptic group. Intervals between the recordings ranged from one to 11 years in three-quarters of the cases and less than one year in the remainder. All patients had undergone continuous treatment with various types of anticonvulsant medication. Ten cases (5 per cent) were completely controlled, but only 3 per cent of these had a normal electroencephalogram. The disappearance of clinical seizures was not limited to any particular age group, nor was it in general related to the frequency or severity of attacks. The highest percentage of cases in whom follow-up studies were obtained showed no change in clinical symptoms or electroencephalographic abnormality.

TABLE 1

TYPES OF CONVULSIVE SEIZURES AMONG PATIENTS WITH SIX PER SECOND SPIKE AND WAVE

| *Diagnosis* | *No. of cases* | *Percentage of total group* |
|---|---|---|
| Epilepsy | | |
| Grand mal | 115 | 55 |
| Psychomotor | 5 | 2 |
| Jacksonian | 3 | 1 |
| Focal | 1 | 1 |
| Petit mal | 0 | 0 |
| Total | 124 | 59 |

TABLE 2

NONCONVULSIVE PAROXYSMAL SYMPTOMS OF PATIENTS WITH SIX PER SECOND SPIKE AND WAVE

| *Symptoms* | *No. of cases* | *Percentage of total group** |
|---|---|---|
| Headache | 46 | 22 |
| Attacks of unconsciousness | 29 | 14 |
| Dizzy spells | 25 | 12 |
| Nausea and vomiting | 14 | 7 |
| Transient visual disturbances | 14 | 7 |
| Paresthesia | 9 | 4 |
| Rage and temper tantrums | 9 | 4 |
| Body pain | 4 | 2 |

*Symptoms are non-exclusive; the percentage cannot be added to give 100 per cent.

ETIOLOGY

Etiologic correlates were sought with the six per second spike and wave pattern, but none could be found. In 85

TABLE 3

NONPAROXYSMAL SYMPTOMS OF PATIENTS WITH SIX PER SECOND SPIKE AND WAVE

| *Symptoms* | *No. of cases* | *Percentage of total group** |
|---|---|---|
| Personality disorder | 25 | 12 |
| Mental retardation | 23 | 11 |
| Strabismus | 9 | 4 |
| Neurosis | 6 | 3 |
| Psychosis | 4 | 2 |
| Memory impairment | 2 | 1 |
| Pupillary disturbances | 2 | 1 |
| Oculogyric crises | 1 | 0.5 |

*Symptoms are non-exclusive; the percentage cannot be added to give 100 per cent.

per cent there was no evidence or presumptive cause. The remaining 15 per cent of patients had a positive history of head trauma or encephalitis directly related to the onset of symptoms. There were no cases of verified brain tumor in this series.

## COMMENT

Although the six per second spike and wave discharge was never observed in immediate temporal association with a clinical seizure, it is nevertheless correlated highly with convulsive seizures and other ictal symptoms. Therefore, it may be considered a type of seizure discharge and treated accordingly.

In order to facilitate the recognition of six per second spike and wave in the electroencephalogram, several factors must be kept in mind. Waking records are inadequate, since the pattern is best seen in drowsiness or very light sleep. Its duration is often less than one second, it may occur quite infrequently, and in adults it is usually of such low voltage as to be easily overlooked by an untrained person.

Two electroencephalographic abnormalities have characteristics in common with the six per second spike and wave. In very young individuals this discharge can be of high voltage and low frequency, resembling the three per second spike and wave pattern of petit mal.[1] However, its formation is never quite as regular as the classical petit mal and it never appears in long bursts or runs. It almost always disappears during sleep and is only rarely influenced by hyperventilation. In no case in the present series was the discharge accompanied by any clinical manifestations, and there were no cases which had a history suggestive of petit mal.

In the adult group there are similarities between the six per second spike and wave and the six per second positive spike discharge.[1] The frequency, duration, and positivity of the spike are similar, but the parieto-occipital distribution that occurs in adults and the maximal frontal discharge which is common in children distinguish it from the six per second positive spike discharge, for the latter is usually of highest voltage in the occipitotemporal area. The fact that the six per second spike and wave rarely appears after the hump phase or in the spindle phase of sleep is also a distinctive feature. Interesting parallelisms, however, are apparent in age distribution and in the clinical correlates. Both types of discharge are commonest in adolescents and young adults, and both are associated with a high incidence of seizures, which in some cases are convulsive but in other cases take the form of one or more of the following: headaches, dizzy spells, vomiting attacks, or a variety of ictal symptoms.

Regarding the prognosis of patients with six per second spike and wave discharge, our information is too limited to permit definite statements, but the cases on which there is follow-up information show that seizures were adequately controlled in only 20 per cent of the group that returned for repeat electroencephalographic studies, in spite of intensive anticonvulsant medication.

It is suggested these cases are more resistant than other types of epilepsy to the drugs that are presently available.

## SUMMARY AND CONCLUSION

The six per second spike and wave discharge is a rare but distinct electroencephalographic abnormality. Among 20,000 recordings with some type of

seizure activity, it was encountered in 210 cases, or 1 per cent. Like other patterns which correlate with epilepsy, it is occasionally encountered in "normal" control subjects and persons without signs and symptoms of brain disorder. The abnormality is primarily confined to the drowsy phase of sleep and shows variations of frequency, amplitude, and distribution in different age groups. It correlates with epilepsy; convulsive seizures occur in almost 60 per cent of the cases and an additional 20 per cent have paroxysmal disorders such as headaches, syncope, attacks of dizziness, and vomiting. The remainder have a variety of psychiatric and neurologic disturbances. The etiology is unknown in most cases. The prognosis is not as good as in some other types of epilepsy. A high percentage of patients are not benefited by presently available anticonvulsant drugs.

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■ Were I writing a book on diseases of the nervous system, I should not have in it distinct sections on diseases of the spinal cord, medulla oblongata, and pons Varolii, but one section including diseases of all these parts, the three morphological divisions being considered together as making up one anatomico-physiological unity. This unity I have called the lowest level of evolution of the central nervous system; it is, I think, pretty much what Marshall Hall named the true spinal system. It is a division of the nervous system complete in itself, in the sense that it represents all parts of the body. It is to a large extent complete by itself; the organic centres on this level are considerably, if not in some cases quite, independent of the higher levels.

A case of bulbar paralysis "complicated" with ordinary progressive muscular atrophy is, so to put it, half in and half out of a section on diseases of the spinal cord; it is well within one on diseases of the lowest level, and, considered as a disease of several motor centres of the same series of this level, is not "complicated." Whilst the anatomist speaks of segments (sensori-motor), we, as medical men, must speak of centres motor and sensory of this level, because, for example, disease may "attack" the motor elements alone of segments. Taking the spinal anterior horns and their higher homologues (nuclei of motor cranial nerves) as making up one homologous series of lowest motor centres all along the lowest level, we have an homologous series – I do not say as yet a complete one – of progressive muscular atrophies, from ophthalmoplegia externa downwards, each owing to atrophy of cells of different lowest motor centres.

J. Hughlings Jackson in *Remarks on the Diagnosis and Treatment of Diseases of the Brain*, published in 1888.

***CASE REPORT***

# Spontaneous Subarachnoid Hemorrhage in Sickle Cell Anemia

*Harold S. Ballard, M.D. and H. Bondar, M.D.**

THAT the central nervous system can be involved during the course of sickle cell anemia is an established fact. The symptoms which have been observed include drowsiness, stupor or coma, hemiplegia, aphasia, headache, convulsions, stiffness of the neck, irritability, nystagmus, pupillary changes, blindness (temporary or permanent), cranial nerve palsies, and paresthesias of the extremities. The lesions in the central nervous system are most often due to thrombosis.[1] Review of the literature has confirmed our impression that massive subarachnoid hemorrhage in sickle cell anemia is extremely rare. In this paper, we present a case in which the clinical manifestations of both diseases are complete.

CASE PRESENTATION

A 25 year old colored man was admitted to the Cumberland Hospital at 9:30 p.m. on June 23, 1955. The patient was completely disoriented and the following history was obtained from relatives. Upon returning home from work about 7:00 p.m. on June 23, 1955, the patient's mother discovered her son lying on the floor with fever and incoherent speech. He had apparently been asleep at the time of the mother's departure for work earlier on the same day. The mother arranged for her son to be transferred to the hospital immediately.

Past history revealed that the patient had been hospitalized seven years previously because of ulcerations over both medial malleoli which were refractory to therapy. At this time patient was discovered to have sickle cell anemia. He was discharged after four months of therapy, at which time both ulcers had healed. Three years following discharge, ulcerations recurred and remained indolent. The remainder of the past history was non-contributory.

Physical examination revealed a well developed and moderately well nourished tall, thin colored man thrashing about in bed and babbling incoherently. There was a slight icteric tinge to the sclerae. Examination of the ears, nose, and throat was negative. Fundoscopic examination revealed moderate pallor of both disks. Moderate nuchal rigidity was present; otherwise the examination of the neck was negative. The lungs were clear to both percussion and auscultation. The heart was not enlarged and the rhythm was regular. Examination of the extremities revealed moderate pallor of the nail beds. Over both medial malleoli there were active round punched-out ulcerations. Neurologic examination revealed hyperactive deep tendon reflexes, bilateral Babinski signs, and positive Kernig and Brudszinki signs.

Spinal fluid examination upon admission revealed grossly bloody fluid in all tubes. Initial pressure was 280 mm. water, closing pressure 190 mm. water. Laboratory examination revealed markedly xanthochromic supernatant fluid with an abundance of sickled red blood cells. Chemistries were as follows: protein 300 mg. per cent; sugar 58 mg. per cent; chlorides 740 mg. per cent. Urinalysis revealed urobilinogen in excess. Hematologic findings were as follows: hematocrit 23 per cent; white cell count 16,000, with polymorphonuclears 79 per cent, lymphocytes 11 per cent, monocytes 7 per cent, and basophils 3 per cent. Sickle cell preparation was reported as 95 per cent sickle

*From the medical service, Cumberland Hospital, Brooklyn, New York.

cells at 24 hours. Three days following hospitalization bilirubin was 6.0 mg. per cent and the icteric index was 60 units.

The morning following hospitalization the patient appeared more comfortable and became oriented. He complained of occipital headaches, nausea, vomiting, and photophobia. Examination of the fundi revealed only disk pallor. Because of vomiting, patient was fed parenterally. Patient was treated supportively with blood transfusions, antibiotics, and vitamins. Hospital course was one of progressive clinical improvement. By the fifth hospital day all neurologic signs had disappeared. A spinal tap performed on the fifth hospital day revealed xanthochromic fluid under an initial pressure of 220 mm. water. Nineteen days following hospital entry a spinal tap was again performed. At this time the spinal fluid was crystal clear and under normal pressure. Cytologic and chemical studies revealed normal findings. The patient was discharged five weeks following hospitalization, at which time hemoglobin was 70 per cent, red blood cell count 3,550,000, and hematocrit 32 per cent.

## SUMMARY

Although Herrick[2] described sickle-cell anemia in 1910, it was not until 1923 that Sydenstricker and associates[3] reported the cerebral manifestations of the disease. Since Sydenstricker's original report subarachnoid hemorrhage has been reported as an infrequent complication of sickle-cell anemia. The literature on the subect is extremely scanty. The clinical manifestations and spinal fluid findings in our case have been summarized above. This is a rather unusual case and, although the possibility of aneurysm exists, the hemorrhagic diathesis of the acute crisis warrants the impression that this is one of the complications of the anemia. This condition exemplifies more than any other how varied the symptoms of sickle-cell anemia can be.

## ADDENDUM

One year has elapsed since the data on this case were compiled. During this time a progress report reveals that the patient is presently asymptomatic. Although his hemoglobin remains low, no crises have occurred during this period. No pathologic sequelae followed the subarachnoid hemorrhage. Cerebral angiography in another institution revealed no evidence of congenital aneurysm.

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■ Galen has presented us with a very clear description of the nervous system. His account of the brain and its membranes, the cerebellum, the medulla spinalis, and the nerves, with the distribution of them to the various parts of the body, is highly interesting; and, all things considered, wonderfully accurate; and his conjectures concering the nature and uses of these organs are very ingenious.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

# Neurology

## BOOK REVIEWS

### Neural Control of the Pituitary Gland

*G. W. Harris, F.R.S., Sc.D., M.D. 1956. London: Edward Arnold, Ltd. $6.75.*

THIS IS A MONOGRAPH with a clearly defined objective, as indicated in its title; it is pleasant to report that the expectation of the book is largely fulfilled. Working in a field in which the author has made numerous contributions, in some instances hitherto unpublished, he gives an excellent brief survey of historic background material and a judicious and fairly adequate presentation of the recent literature. Some of the older basic anatomic and physiologic reports are not always included.

The reviewer was particularly impressed with the author's concern for definition and with his clarity of description. It is interesting to note how investigations in this field are weighted; 12 chapters are devoted to modes by which the nervous system affects the pituitary gland and through it other hormone systems, while only one chapter is devoted to the effect of hormones on the central nervous system. The minimal amount of information that we have in this latter connection is doubly interesting, since it is in this phase of the cycle that we have the striking effects of the internal secreting glands on behavior. That the hormonal affective circuit involves the hypothalamic mechanism is clearly demonstrated by the evidence presented.

The author gives a well-balanced account of the basic anatomy of the hypothalamus and the pituitary gland. This is a particularly valuable contribution since the author takes a position and defends by excellent reasoning his view in the disputed matter of the direction of flow in the portal circulation between the hypothalamus and the pituitary. In general, the theory is put forth that nerve fibers from the hypothalamic nuclei liberate the humoral substance into the capillaries of the primary plexus in the median eminence to be carried by portal vessels to the anterior pituitary for excitation or inhibition of its secretions.

The evidence for the activation or inhibition of the individual pituitary hormones in all three portions of the gland and the cycle of effects on their target organs is presented. The hypothalamic mechanisms influencing gonadal, thyroid, and adrenal activity are described in detail and generally indicated by diagrams.

Because of the detailed factual presentation, the book is not one that can be skimmed lightly; it is carefully assembled and documented and emerges with a logically established viewpoint of the structure and interrelated function of the hypothalamic and pituitary system. It is regarded as an

important reference work for clinical and laboratory workers in the field and one which will serve to bring the reader up to date on the reciprocal effects exerted by the central nervous system and the endocrine glands.

A. R. V.

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## Neurology of the Ocular Muscles

*David G. Cogan, M.D. Second edition, 1956. Springfield, Illinois: Charles C Thomas, Publisher. 296 pages. $8.50.*

THE FIRST EDITION of Dr. Cogan's *Neurology of the Ocular Muscles* was published in 1948 and was an important contribution to the study of neuro-ophthalmology. The second edition follows virtually the same plan as the first, but current advances in medical knowledge have been incorporated both from clinical and from anatomic and physiologic points of view. For instance, the section on the cerebellum has been expanded to cover recent advances in the recognition of anatomic and functional localization in this structure and the ocular components of cerebellar disease, and internuclear ophthalmoplegia has been treated in considerably more detail in view of its importance as an ocular manifestation of multiple sclerosis.

This book incorporates a detailed clinical and anatomic study of the neurology of ocular movement and the importance of disturbances of ocular motility in the diagnosis of both neurologic and ophthalmologic disease. It is of great importance both to the neurologist and the ophthalmologist.

R. N. DE J.

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## Neurochemistry

*Edited by Saul R. Korey, M.D. and John J. Nurnberger, M.D. 1956. New York: Paul B. Hoeber, Inc. $6.75.*

THIS WORK presents the contributions of 23 investigators in a symposium on the chemistry of the nervous system. It forms an introduction to the rapidly developing newer approaches to the study of the nervous system based on biochemical activity and on the alteration of that activity in various diseased states.

A work such as this naturally presents rather scattered material and sometimes assumes a knowledge of basic biochemical data which are not in the immediate possession of the clinical neurologist. However, it is not the plan of this book to do more than to present a series of representative essays.

The contribution of Palay on the structure and function of the neuron, Tower on the neurochemistry of seizures, Kennedy on cerebral metabolic rate in children, and Sokoloff on the relation of cerebral circulation and metabolism to mental activity are of general interest, and papers by W. Henberg, Brady and Stadtman, Porter and Folch-Pi, Scheinberg, Gordon, Jordon, Rich, Nurnberger, Korey, Wilson, and Goldstein present more specific topics and specialized aspects of the subject.

Of particular importance is the timeliness of this volume, since it coincides with the establishment of a section on neurochemistry within the American Academy of Neurology and serves to emphasize the growing importance of this field in the understanding of the nervous system.

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JUNE 1957

**Forster Becomes AAN President** At the ninth annual meeting of the American Academy of Neurology held in Boston (April 22-27), Francis M. Forster took office as AAN president (1957-59), succeeding Walter O. Klingman.... Other newly elected officers are Augustus S. Rose, president-elect; A. L. Sahs, vice-president; Joseph M. Foley, secretary; and Charles Van Buskirk, treasurer.... Added to the board of trustees were Knox Finley and Joe E. Brown to fill the expired terms of Luman E. Daniels and A. R. Vonderahe, respectively. Arnold P. Friedman was elected to fill the unexpired term (two years) of Robert W. Graves, who has resigned because of ill health.... The new slate of officers was presented to the membership by the nominating committee chairman, Howard D. Fabing, and passed by unanimous acclaim.

**Committee Chairmen Named** Acting with nimble dispatch, President Forster has appointed the chairman of AAN committees who will serve during his term of office. They are: Royal C. Gray, auditing; A. B. Baker, liaison with community and voluntary health organizations; Sidney Carter, constitution and by-laws; Lee M. Eaton, ethics; A. T. Steegmann, history; Pearce Bailey, international collaboration; F. M. Forster, joint committee on neurologic education (AAN and ANA); R. N. DeJong, editor-in-chief, Neurology; L. T. Kurland, nomenclature and biometrics; A. R. Vonderahe, nominating; Pearce Bailey, membership; Maynard M. Cohen, placement; F. L. Stone, program; Charles Rupp, local arrangements; G. H. Glaser, scientific meetings; L. D. Boshes, scientific exhibits; H. D. Fabing, public relations; F. O. Meister, registration; Ward Halstead, research; and A. B. Baker, special courses.... President Forster combined the legislative committee and the committee on legal aspects of neurology into a single committee on legislation under the chairmanship of Howard D. Fabing. He also created a new committee on neurology in the federal services under Benedict Nagler.... As is the custom, various committee chairmen will submit to the president a panel of members whom they wish to have serve on their respective committees.

**Boston Meeting Largest Ever** About seven hundred AAN members, exclusive of the Woman's Auxiliary and guests, registered for the 1957 meeting at Boston's Sheraton Plaza (April 22-27), almost double any previous Academy meeting registration. At the scientific sessions 132 papers were presented,

including 32 papers from the newly created section on neurochemistry. An impressive array of exhibits, demonstrations, and motion pictures strategically occupied the foyer and many of the salons in the hotel. Paul I. Yakovlev's remarkable exposition of the anatomy of the brain was housed in the Warren Anatomical Museum of the Harvard Medical School.... A 1957 innovation was the first Academy prize award for the best scientific exhibit, which went to Madge E. and Arnold B. Scheibel for their display on the Substrates of Integration in the Brain Stem Recticular Core. The award was made by Benjamin Boshes at the annual banquet (April 26).... The annual prize award by the Woman's Auxiliary to the junior member submitting a manuscript, which was judged best by a prize committee of the officers and board of trustees, was presented this year to Ernst A. Rodin of the University of Michigan. Dr. Rodin presented his essay on the EEG Syndrome which correlates with severe disruption of personality structure, prior to the presidential address by Walter O. Klingman at the opening of the scientific sessions, April 25.... Among the honorary-corresponding members present at the meeting were: Dr. Gunnar Wohlfart, Lund, Sweden, who delivered the Robert Wartenberg Memorial Lecture, and Dr. E. Tchehrazi of Iran.... In spite of its size, the meeting proceeded deftly and on time, thanks to the diligent preparations of Frederick L. Stone (general program), Joseph M. Foley (local arrangements), James L. O'Leary (scientific program), and Louis D. Boshes (exhibits and demonstrations).... The 1958 annual meeting is scheduled to be held at the Bellevue Stratford Hotel, Philadelphia (April 21-26).

**Special Courses Reach New High** There were 422 registrants, the largest number to date, for the 1957 special courses which preceded the annual meeting in Boston. In 1958 in Philadelphia, there will be ten special courses as follows: neuropathology (F. Y. Tichy), EEG (Frank Morrell), advances in neurology (Joe E. Brown), physiology and diseases of the cerebral circulation (A. L. Sahs), ultrastructure of the nervous system (W. F. Windle), disorders of movement (C. A. Kane), pediatric neurology (Sidney Carter), neuropharmacology (D. B. Tower), neuroophthalmology (N. S. Schlezinger), and neurology for the general practitioner (Benjamin Boshes.)

**Mrs. Sagebiel to Lead Woman's Auxiliary** At the AAN annual meeting, the Woman's Auxiliary elected Mrs. James L. Sagebiel, president; Mrs. A. L. Sahs, president-elect; Mrs. R. N. DeJong, vice-president; and Mrs. Joseph L. Whelan, secretary. Mrs. D. B. Ruskin was reelected treasurer.

* * * * * *

**Important Announcement From P and N Board** David A. Boyd, Jr., secretary-treasurer of the American Board of Psychiatry and Neurology, announces that the next board examinations will be held in New York City (Dec. 16-17, 1957) and

in San Francisco (Mar. 17-18, 1958).... Also, beginning with the 1957 (New York) examinations and applying to neurologists only, there are changes in the examination procedures in basic neurology. Instead of the previous two duplicate one-hour examinations in basic neurology, candidates for certification in neurology will have two one-hour examinations in basic neurology, wherein one examination will be in gross and microscopic pathology and neuroanatomy and the other examination will be in neuroroentgenology, neurophysiology and EEG, neurochemistry, neuropharmacology, and clinical diagnostic testing.

**Fund Proposed for Creation Of a Sherrington Lecture**

In this centenary year of the birth of Sir Charles Scott Sherrington, a founder of the physiology of the nervous system, the Royal Society of Medicine wishes to pay tribute to his life and work by raising a fund toward a Sherrington Lecture to be delivered from time to time in the society's rooms in London. The Sherrington Lecture will be devoted to a furtherance of knowledge on the nervous system.... The Royal Society of Medicine feels that many will wish to contribute to this effort, both those who were Sherrington's friends, pupils, and colleagues, and those, more numerous, who, as patients, doctors, and scientists, have benefited indirectly from his work.... Donations should be made payable to the Secretary, The Royal Society of Medicine, 1 Wimpole Street, London, W.1, and checks crossed "Sherrington Memorial".... The endeavor of The Royal Society is commended by a distinguished and widely representative group of scientists. Among them are Sir Russell Brain, Sir Lindor Brown, Professor John Fulton, Mr. W. R. Henderson, Professor Sir Cyril Hinshelwood, Professor E. G. T. Liddell, Mr. D. W. C. Northfield, Sir Clement Price Thomas, Sir Charles Symonds, and Sir Francis Walshe.... The name of Sir Charles Sherrington is to be honored both at the Anglo-American Symposium on Knowledge of the Brain (London, July 15-18) and at the First International Congress of Neurological Sciences (Brussels, July 21-28), where the first joint meeting of the congress on extrapyramidal pathology is dedicated to his memory.

**New AAN Members Widely Distributed**

As of April 1, over 750 physicians and scientists have accepted membership in the Academy since the St. Louis meeting in 1956; 725 of these new members have been tabulated according to category, geographic distribution, and affiliation with a medical or scientific discipline. The new group includes nine fellows, 57 actives, 171 juniors, and 459 associates, the majority coming from 41 states and Canada and a few from Central America, South America, Europe, Egypt, Iran, and Israel.... The six leading states for this new group are New York (132), Maryland (63), Massachusetts (53), Pennsylvania (43), California (42), and Illinois (33), and 25 are from Canada.... Of the new members tabulated above, 441 belong to clinical disciplines, 39 to clinical laboratory disciplines

(chiefly EEG and clinical neurophysiology), and 200 are basic neurologic scientists. Among the clinicians, the top six groups are neurologists (306) which includes the 171 new juniors; neurosurgeons (36), pediatricians (29), internists (22), and ophthalmologists (15). Among the basic scientists are neuroanatomists (62), neurophysiologists (46), neuropathologists (34), neurochemists (10), pharmacologists (8), and biophysicists (6).... The above list also contains four new honorary members and 25 new honorary-corresponding members.... Among the new members are three Nobel laureates.

**355 From U. S. Registered For Brussels Congress** Three hundred and fifty-five Americans have registered through the U. S. secretary for the Sixth International Neurological Congress for the First International Congress of Neurological Sciences to be held in Brussels (July 21-28), as compared to the 159 registered at a comparable time for the previous neurologic congress held in Lisbon in 1953. Of this number, 224 are registered as active members, 38 as associates, and 93 as auxiliary. Among the 262 actives and associates, 171, or 65 per cent, are Academy members.

**Briefs** A division of neurology has been established at the Western Reserve University Medical Center in Cleveland, with Clark T. Randt as director. The clinical neurology service will comprise 122 beds and a large out-patient unit. Basic science instruction, research opportunities, and special training in EEG and EMG are provided.... A clinic for muscular dystrophy patients has been established at the University of Oregon Medical School under Roy L. Swank, head of the department of neurology. The clinic is sponsored by the Portland Chapter of the Muscular Dystrophy Associations of America.... Lewis J. Doshay lectured on Parkinson's disease at the First International Congress of Therapeutics in Utrecht, Holland.... From Leiden, Holland, comes the tragic news of the sudden death of Prof. Dr. G. G. J. Rademaker.

Percival Bailey

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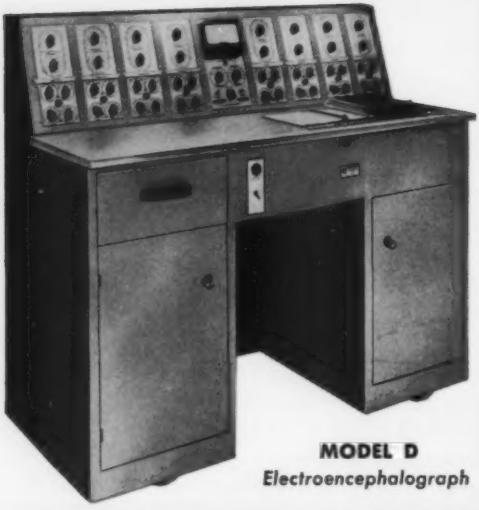

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